The Independent
MEDICINES & MEDICAL DEVICES
Safety Review

The Independent Medicines and Medical Devices Safety Review

Written Evidence

Public Bodies

Published December 2018

Updated January 2019

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WARNING: Please be aware some evidence contains descriptions, pictures and audio of the harm suffered by individuals. Some may find this distressing.

Commission on Human Medicines – Expert Working Group on Hormone Pregnancy Tests

COI:

To reassure Ministers and the public that the advice on which decisions about medicines is based is impartial, it is important to have in place a robust policy governing the declaration and management of relevant interests. In the interests of transparency and accountability, this Code of Practice, the declarations made by 2 chairmen and members of the various committees, and the actions taken to manage potential conflicts of interest are made public. In addition, where an individual has declared in advance of a meeting an interest that would exclude him or her from the relevant discussions, this information will be used by the secretariat to ensure that, wherever possible, the relevant committee papers are not sent to that individual.

The full Code of Practice for Chairmen and Members of the Commission on Human Medicines, Certain Committees and Expert Advisory Groups, can be found here:

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/440853/CHM_code_of_practice.pdf

Submission:

Dear Dr Brasse

Reference number: CYTZFA

Thank you for your letter of 19th September 2018 to MHRA Customer Services. This has been forwarded to me, as Chair of the Commission on Human Medicines (CHM) and Dr Ailsa Gebbie, as Chair of the CHM Expert Working Group on Hormone Pregnancy Tests (HPTs), for a reply.

It may be helpful to give a brief overview of the work of the CHM on HPTs. In 2015 at the request of Ministers the CHM set up an Expert Working Group and appointed Dr Gebbie to act as Chair. The purpose of the Group was to review all the available evidence on a possible association between HPTs and adverse outcomes of pregnancy and to make recommendations. The report of that review, together with all the evidence considered by the Group, was published on the CHM website in January 2018. We believe that a full chronology of events is being provided by the MHRA in its response to your request for information.

In February 2018, in response to the publication of a study of the components of Primodos (a HPT) in zebrafish by *Brown et al*., the CHM established a new ad hoc Expert Group. None of the experts on this Group were involved in the previous HPT review. The Group met to discuss the zebrafish publication on 5th October and was Chaired by Professor Alan Boobis. We believe a member of your review team, Sonia MacLeod, attended the meeting as an independent observer. Mrs Lyon, Chair of the Association for Children Damaged by Hormone Pregnancy Tests also attended as an observer. Mr Dobrik of the Thalidomide Trust's National Advisory Council was also invited to observe but did not attend on the day. Professor Vargesson, the lead researcher gave a presentation to the Group and stayed to discuss the study and its findings with them.

On 11th October the CHM, joined by Professor Boobis by telephone, reviewed and endorsed the draft meeting minutes of the Group. The CHM concluded that while well-conducted, there are no

implications from the publication of Brown et al. for the clinical use of medicines currently on the market.

We are aware that the publication of Brown et al. was also considered by the European Committee for Medicinal Products for Human Use (CHMP) at its meeting in October. Although the report of the review has not yet been made publicly available, we believe its findings are consistent with those of the ad hoc working group chaired by Professor Boobis.

Your letter of 19th September asks two specific questions about the original Expert Working Group:

1. Please can you describe the governance process around the EWG established October 2015?
2. How were the Terms of Reference drawn up, and what were the reasons it was amended?

In response to your first question, the governance process for the Expert Working Group on HPTs followed the requirements set out in the Human Medicines Regulations 2012 (Part 2) on the CHM and its expert advisory groups, whereby:

i. the Minister, as the Licensing Authority, directed the CHM as the 'advisory body' to appoint an expert advisory group in the form of the Expert Working Group on Hormone Pregnancy Tests, to conduct a review
ii. the CHM was consulted on the draft terms of reference for the Group and the membership, and appointed Dr Gebbie as the Chair
iii. the EWG conducted the review, reached recommendations as set out in its report and provided its advice to the CHM
iv. after careful consideration of the report the CHM fully endorsed its conclusions and recommendations and gave its advice to the Minister
v. the report was published in the House, accompanied by a Written Ministerial Statement.

Regarding the terms of reference of the Group, these were agreed in the same way as all Expert Working Groups, including their consideration and endorsement by the CHM.

At its meeting in December 2014 the CHM endorsed the draft terms of reference of the EWG on HPTs:

- To consider all available evidence on the possible association between exposure in pregnancy to HPTs and congenital abnormalities in the child, including consideration of any potential mechanism of action
- To consider whether the Group's findings have any implications for currently licensed medicines in the UK or elsewhere and
- to make recommendations.

These draft terms of reference set out the broad scope of the review, with respect to the evidence that would need to be considered in relation to the possible association between HPTs and congenital anomalies, as referred to by MPs and the Minister in the October 2014 House of Commons debate.

The draft terms of reference were subsequently confirmed by the Minister in a letter to Yasmin Qureshi as Chair of the APPG in September 2015. The Minister continues: "It is important to review the scientific evidence [on a possible association] to establish whether there is any causal association between use of HPTs and subsequent birth defects in the child".

At its first meeting in October 2015, the terms of reference were discussed by the EWG. The Group suggested they could be amended to more widely capture adverse effects on pregnancy (rather than limiting only to congenital anomalies) as well as to capture what lessons may be learnt to improve current regulatory systems and processes. The amended terms of reference were agreed unanimously by the Group at its second meeting in December 2015 as follows:

- To consider all available evidence on the possible association between exposure in pregnancy to hormone pregnancy tests (HPTs) and **adverse outcomes in pregnancy (in particular congenital anomalies, miscarriage and stillbirth)** including consideration of any potential mechanism of action
- To consider whether the EWG's findings have any implications for currently licensed medicines in the UK or elsewhere
- **To draw any lessons for how drug safety issues in pregnancy are identified, assessed and communicated in the present regulatory system and how the effectiveness of risk management is monitored**
- To make recommendations.

Having been endorsed by the Expert Working Group at its second meeting in December 2015, the terms of reference were not further amended. The discussions of the Expert Working Group around the terms of reference are documented in the published minutes (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/667482/Minutes-declaration-of-interests-redacted.pdf).

It is important to highlight that the terms of reference of the CHM Expert Working Group set out the scope of the issues to be considered by the Group; they did not define the conclusions that might be reached. Implicit and integral to any scientific assessment of evidence on medicines and harms is to see whether the medicine is responsible for causing the harm (i.e., a causal association) rather than simply being associated with it (and potentially the result of an alternative factor, i.e. a chance finding not associated with administration of the medicine). To achieve this the strengths and limitations of all the available data on a possible association had to be carefully considered by relevant experts with the benefit of up-to-date knowledge and experience.

Based on the quality and strength of the available scientific evidence the EWG considered that, taking all aspects into consideration, it did not support a causal association between the use of HPTs, such as Primodos, during early pregnancy and adverse outcomes, either with regard to miscarriage, stillbirth or congenital anomalies.

We very much hope that you find this information helpful but please do not hesitate to get in touch should you require any further information.

Yours sincerely,

Professor Stuart H Ralston, MD, FRCP, FMedSci, FRSE
Chair of the Commission on Human Medicines

Dr Ailsa Gebbie, MB ChB FRCOG FRCP(Edin) FFSRH
Chair of the Expert Working Group on Hormone Pregnancy Tests

MHRA

COI:

The MHRA is an Executive Agency of the Department of Health and Social Care. We are part of the Civil Service and support the Government of the day in developing and implementing its policies, and in delivering public services. Our staff are accountable to ministers and are committed to carrying out their roles with dedication and a commitment to the Civil Service and its core values: integrity, honesty, objectivity and impartiality. We are also a trading fund and operate on a cost recovery model, and, as with all regulators, we have connections with those who we regulate and have policies and procedures in place to ensure we remain objective and impartial.

The MHRA is responsible for:

- Assessing the safety, quality and efficacy of medicines, and authorising their sale and supply in the UK.
- Carrying out post-marketing surveillance of medicines and medical devices, monitoring adverse reactions and taking action to safeguard public health.
- Operating a separate safety reporting scheme for haemovigilance for the reporting of serious adverse reactions and events related to blood safety and quality.
- Testing medicines to identify and address quality defects, monitoring the safety and quality of imported medicines, investigating internet sales and counterfeit medicines.
- Ensuring compliance with UK and European standards through inspection and enforcement.
- Managing the British Pharmacopoeia (BP)
- Overseeing the UK bodies that audit medical device manufacturers, operating a compliance system for medical devices, and contributing to the development of standards for medical devices.
- Providing expert scientific, technical and regulatory advice on medicines and medical devices.
- Regulating clinical trials of medicines and approving clinical investigations of medical devices.
- Promoting good practice in the safe use of medicines and medical devices, and providing information to help inform treatment choices.

Financial:

The Government trading fund that finances the Agency was established by the Medicines and Healthcare products Regulatory Agency Trading Fund Order 2003 (SI 2003/1076), made under the Government Trading Funds Act 1973.

Where the Secretary of State has functions under UK legislation relating to medicines, medical devices and blood, these are performed by the Agency.

The areas in which the Agency operates (including medicines, medical devices and blood) are predominantly the subject of EU legislation, as it applies to and is implemented in the UK.

Medicines regulation is funded entirely from fees. In setting its fees the Agency takes account of full cost recovery rules as set out in HM Treasury's *Managing Public Money*.

Devices regulation is primarily funded through a service level agreement with the DHSC with approximately 10% of its revenue from fees charged to recover costs incurred by the Agency to do the vital work it covers. As we are not directly involved in approving or assessing medical devices before they are placed on the market, we do not receive money from manufacturers of medical devices on this basis.

Handling of declarations and conflicts of interest:

Given the specialist nature of the MHRA's work, a proportion of our staff are recruited from, or have past employment in, the pharmaceutical industry and/or medical devices industry. First-hand knowledge and experience of these sectors is essential for effective regulation.

In the interests of openness and accountability and to protect staff and the Agency from possible accusations of inappropriate behaviour, the Agency maintains a register of all financial interests in the pharmaceutical and healthcare (medical devices) industries held by staff and members of their immediate family and also of any other relevant interests.

Without exception, all members of Agency staff are required to immediately declare any financial or other interests as and when they arise and make a declaration every year even if a nil response.

In addition to declaring financial interests, members of staff also consider whether there is any other matter which could be regarded as affecting their impartiality, whether this be in relation to pharmaceutical or medical devices work, or the research and scientific work the Agency is involved in.

Staff members can't hold direct financial interests in the pharmaceutical and healthcare (medical devices) industries.

Newly appointed staff will be required to dispose of such interests before taking up employment with the Agency. Exceptionally a transition period of no more than 3 months may be agreed with the Divisional Director. In such cases the interests must be declared on the Conflict Of Interest (COI) register. Similarly, staff may not hold any employment or directorships in the pharmaceutical or healthcare (medical devices) industries, nor carry out consultancy or other private work for those industries.

Information in relation to our decisions is made available unless it cannot for legal or other respect, commercially sensitive information.

Medicines & Healthcare products
Regulatory Agency

Independent Medicines and Medical Devices Safety Review – Call for Evidence

31 October 2018

Executive Summary

The MHRA welcomes the opportunity to contribute to the Independent Medicines and Medical Devices Safety Review into the handling by the healthcare system of three particular medical interventions and to offer suggestions about ways of improving public engagement and collaboration between the different bodies that provide patient care.

Listening to patients must be at the heart of healthcare. A patient's 'journey' can be complex and lengthy, with safety issues spanning many bodies within the complex healthcare system. We know one of the frustrations of patients is navigating this complexity.

The MHRA's core role is the regulation of products, rather than clinical practice or the provision of healthcare. It already does much to engage and listen to patients and their representatives through, for example, the Patient Group Consultative Forum, topic specific stakeholder meetings, lay representation on advisory committees, open Board meetings, patient reporting of adverse drug reactions and adverse incidents, and individual meetings with patients.

No effective medicine or medical device is completely free of risk. As a regulator, our work must be underpinned by robust and fact-based judgments to ensure that the benefits justify any risks. Decisions are not always straightforward. They are inevitably based on data which includes a range of individual experiences, either of benefit or of risk. Independent expert advice, including lay representatives and, in some cases, the direct input of patients is sought to ensure that risks are well characterised and communicated. An ongoing challenge is that safety evidence accrues over time and can change. Therefore, the balance of risks and benefits may change over time, necessitating continual review of the evidence.

The MHRA is a world-leader in evaluating and communicating the benefits and risks of medicines and medical devices and the methods we use (with ever greater patient participation) have evolved over time.

The MHRA's general approach is as follows:

- One of our main aims is to identify and communicate effectively and quickly problems associated with medicines and medical devices. The Agency is a recognised global leader and was first to identify many important safety issues and develop systems and legislation to improve safety monitoring.
- The voices of patients and their families play a vital role in our work, through patient reporting, consultation and collaborative working in specific areas, including safety issues. Patient concerns are heard in an open, fair and accessible way.
- We are committed to ensuring that patient concerns are acted upon appropriately, and as swiftly as possible and in a coordinated fashion, but this can sometimes be challenging, because many different stakeholders or interested parties can be involved with differing roles, responsibilities and priorities.
- As a regulator our responsibility is to provide up-to-date and authoritative information to help patients and healthcare professionals make the best choices for each individual.
- In relation to the effectiveness of the relationships between MHRA and commercial interests, the MHRA works with industry to ensure they are compliant with their obligations and has powers to take action in cases of non-compliance. The MHRA also has conflict of interest policies in place.

Lesson learned and suggested improvements for the future:

- A more structured approach to proactive patient engagement and improved safety messaging across the health and care system would be beneficial and we will continue to work with others to develop this to deliver the most effective messaging.

- Given the complexity of the healthcare system, there needs to be clear accountability and leadership, with effective communication and co-ordinated action to minimise harm.
- We are committed to working collaboratively with partners in healthcare including patient organisations to make sure that safety messages reach all those who need to receive them and are acted upon, with feedback on implementation and outcomes. This will require improvements in co-ordination, leadership and accountability.

Valproate

Valproate is an effective treatment for epilepsy and bipolar disorder. It is one of the most commonly used anti-epileptics and it may be the only effective treatment for some patients. Use of valproate was, however, already known to be associated with birth defects when it was first licensed in the 1970s and further evidence has emerged since then about other adverse effects, in particular neurodevelopmental disorders in children exposed if used during pregnancy. We believe that the case of valproate highlights the challenges associated with an evolving evidence base over many years, particularly with an established medicine that has both serious risks and can be life-saving.

Clear warnings about the risk of birth defects associated with valproate were present in the information for healthcare professionals at the time of licensing. Additional warnings have been updated and communicated on numerous occasions since then in response to new and emerging evidence over time and following extensive scientific reviews. Warnings about birth defects were issued in 1982; information on neural tube defects and recommendations for diagnostic screening were added in 1990, warnings on birth defects were expanded in 2001; warnings about developmental delay were added in 2003 and autistic spectrum disorder in 2010. The MHRA has been particularly active in responding to the emerging evidence on the risks of valproate in pregnancy and, given the increasing concerns, the Agency triggered and led the 2014 EU-wide review of valproate and the risk of neurodevelopmental disorders.

The MHRA's approach to regulatory decision-making in relation to the risks of valproate in pregnancy has been characterised by:

- Stakeholder and patient engagement have been integral throughout the evaluation of the emerging safety issues.
- Our approach has been informed by the evolving evidence base, expert groups of the Commission on Human Medicines and by a Valproate Stakeholder Network, including patient groups, set up in 2016 and meeting regularly since then. Patient input has been invaluable throughout the process, both as a source of evidence and feedback on implementation of regulatory measures.
- It became evident from our monitoring that providing health professionals with information, even when repeated through multiple sources, was not changing prescribing behaviour sufficiently.
- The Agency brought these concerns back to Europe and sought agreement for the need for a strengthened regulatory position, supported by a formal pregnancy prevention programme, annual specialist review coupled with an acknowledgement of risk form, and clear valproate labelling and packaging.
- The goal of the current regulatory position is to rapidly reduce and to eliminate pregnancies exposed to valproate, supported by proactive monitoring using real world data.

  The MHRA fully recognised that critical to achieve harm reduction is improving communication and awareness about the risks of valproate during pregnancy:

- The 2014 EU-wide review resulted in extensive work to communicate updated advice to health professionals and patients.

- The need for patients to be provided with information about their medicine and risks is underpinned by legislation.
- Ensuring the patient's understanding of the risks and the need to take effective contraception is now a priority.

Lessons learned and suggested improvements for the future:

The MHRA accepts that there are important lessons to be learned from valproate and improvements needed for the future:

- There is a need for the system as a whole to ensure compliance with the provision of information to patients, specialist review and use of the acknowledgement of risk form and, as a result, enrolment in the Pregnancy Prevention Programme, and we are following this up urgently. A concerted effort by healthcare system organisations and professional bodies is needed to effectively implement this change.
- The Agency will build on the experience it has gained to further strengthen: how we engage with patients and gain a full understanding of the impact of safety issues related to medicines; our interaction with healthcare professionals and co-ordination of action with organisations responsible for delivering healthcare; and our methods of monitoring the effectiveness of our regulatory risk minimisation measures, including how these are communicated and acted upon.

Hormone Pregnancy Tests

Hormone pregnancy tests, such as Primodos, were widely used in the 1950s, 1960s and 1970s to diagnose pregnancy and to treat secondary amenorrhoea. This was at a time when the social, medical and regulatory environment was very different from today. In 1972, following the introduction of medicines regulation, Primodos was licensed by the Department of Health and Social Security for the treatment of secondary amenorrhoea only.

Between 1967 and the 1980s a great many studies on a possible link between hormone pregnancy tests and adverse pregnancy outcomes were published with conflicting findings, giving rise to historical uncertainty around a possible link between hormone pregnancy tests and birth defects.

Evidence on a possible association between hormone pregnancy tests and adverse pregnancy outcomes has been reviewed a number of times in the UK. All reviews consistently found that the available evidence did not support a causal association and had no implications for the clinical use of medicines currently on the market.

UK reviews before 2015:

- by the CSM between 1967 and 1978, when Primodos was withdrawn from the UK market. Despite uncertainty over the evidence, the Committee on Safety of Medicines took a series of precautionary actions as new data emerged to protect women from any possible risk and to remind prescribers that HPTs should not be used to diagnose pregnancy.

- by the MHRA in 2014 in response to a request by Dan Poulter MP, then Parliamentary Under Secretary of State for Health.

The Commission on Human Medicines (CHM) Expert Working Group 2015:

In response to public and political concern, the CHM established an Expert Advisory Group to review the available data on possible association between hormone pregnancy tests and adverse outcomes in pregnancy, and to make recommendations to Health Ministers. Points to note are that:

- The terms of reference of the Group were agreed in the same way as all CHM Expert Working Groups. At the first meeting in October 2015, the terms of reference were discussed and amended, largely at the request of the patient representatives, to broaden

capture of adverse effects on pregnancy and to assess lessons learnt to improve regulatory systems and processes. The amended terms of reference were agreed unanimously at the Group's second meeting in December 2015.

- It was always made clear that issues of historic regulatory process or clinical practice were outside the scope of the review.
- Based on an extensive and careful review, the overall conclusion of the Group was that the totality of the available scientific evidence does not support a causal association between the use of hormone pregnancy tests and adverse outcomes during early pregnancy, and any association was more likely to have been due to chance or to other factors.
- The report of the Group, together with the minutes, declarations of interest and all the evidence considered (which has been reviewed in line with duties under data protection legislation, and common law duty of confidence) is published online.

Reviews in 2018 of a study in zebrafish:

- by a CHM Expert Group of toxicologists at the request of Lord O'Shaughnessy, Parliamentary Under Secretary of State for Health.

- by the EU Committee for Medicinal Products for Human Use (CHMP) under Article 5(3) of Regulation (EC) No. 726/2004.

The healthcare environment has changed significantly since hormone pregnancy tests were first used. There have been substantial advances in all areas of the development, legislation, regulation, study and use of medicines since then. Nonetheless the MHRA accepts that there are important lessons to be learned from the review of HPTs and improvements needed to further strengthen regulatory systems in particular those which aim to protect women from adverse effects of medicines in pregnancy:

- Best practice today is that no drugs should be prescribed in pregnancy unless they are essential for the wellbeing of the mother.
- The focus should now be on implementing the review's recommendations which will help further strengthen the systems in place for detecting, evaluating and better communicating risk with exposure to medicines in pregnancy.
- The case of Primodos highlights the challenges associated with mediating a disagreement over the interpretation of the evidence. The experience has been valuable in terms of the lessons learned regarding the process. In view of the unintentional distress felt by the families, MHRA has apologised and reflected on this experience and is introducing changes to how it interacts with patients and carers.
- In future we will ensure that the information and support given to attendees ahead of meetings/events is reviewed to ensure that it explains as clearly as possible the nature of the meeting, how it will be conducted and what to expect. Sufficient time will be dedicated to listening to the experiences of individuals who attend an expert group to ensure all feel that their concerns have been recognised, understood and will be taken fully into account in decision making.

Abdominal and vaginal pelvic mesh

Surgical meshes have been used since the 1950s to repair abdominal hernias and they were introduced as options for urogynaecological surgery in the 1990's. Mesh is a term used to describe a range of synthetic or biological permanent implants that can be used to provide additional support when repairing weakened or damaged tissue.

Concerns have been rightly raised over complications following procedures where mesh is used in surgery to treat pelvic organ prolapse and stress urinary incontinence; these conditions can both be significantly debilitating. However, it is important that mesh repairs

for pelvic organ prolapse and for stress urinary incontinence are considered independently and separately because the two conditions are quite different; a variety of different mesh repairs are used; and the outcomes may differ substantially for the two conditions.

We recognise some women develop serious complications related to procedures involving meshes, and these can be very distressing. However, we also know many women derive great benefit from these mesh procedures which are used to treat what may be extremely debilitating conditions.

As with any medical device, their use carries the risk of complications and they occur with all types of surgery varying with time and anatomical location. The spectrum of complications is well known for these procedures and the nature and severity depend on a number of factors. These include the pre-existing health of the patients, the complexity of the medical condition being treated, the surgery being undertaken, the skill/training of the surgeon and in surgery using medical devices; the particular device being used and finally the overall healthcare system in executing the chosen options. The majority of the conditions being treated with these devices are highly complex.

We recognise that the regulatory term; 'benefits outweigh the risk' or 'constitutes acceptable risks when weighted against the benefits to a patient' may be interpreted differently by some patients and patient groups. It is clear from some of the reports we have received, that they quite rightly feel the benefits did not outweigh the risks for them. Post-operative perception of the benefits and risks associated with mesh implantation would be very different in someone with complications compared to someone who underwent a successful procedure.

Even if every conceivable safety measure is performed there will always remain an element of 'risk' associated with the use of medical devices and surgery, however small. The final decision of what is an acceptable risk for any condition and for any individual patient ultimately rests with the clinician and patient, and this is at the heart of the informed consent process, supported by information within the manufacturer's instructions made available to clinicians.

Reviews and action taken:

- Since 2010 we have continued to look at many sources of evidence as part of ongoing market surveillance of mesh to treat prolapse and incontinence. When used as part of an appropriate treatment pathway, in accordance with the manufacturer's instructions, the overall conclusion is the totality of the available evidence does not support regulatory action against any mesh manufacturer to restrict or stop their use. We continue to keep this area under review to protect public health.
- We have taken a number of actions to investigate and address an increase in reporting over time as well as highlighting the issues and working with others to consider their place in appropriate treatment pathways. This includes raising awareness of reporting adverse incidents to MHRA, extensive stakeholder engagement, influencing EU regulation and participation in relevant NICE Interventional Procedures Guidance (IPG) programme, Scottish Independent Review (noting the recently published Investigative Review by Professor Britton) and NHS England Working Group Report. This resulted in extensive work by us and others to communicate updated advice and key messages to health professionals and patients.
- NHS England Mesh Working and Oversight Report, Scottish Independent Review and the relevant NICE Interventional Procedures Guidance programme have all concluded there remains a clinical need for mesh repair procedures in appropriate treatment pathways which have also been considered by clinicians and the professional bodies who represent them. This is broadly reflected in NHS's high vigilance scrutiny programme in response to the IMMDS Review's pause conditions.

The MHRA accepts that there are important lessons to be learned from abdominal and vaginal pelvic mesh and improvements needed for the future:

- The MHRA continues to support implementation of NHS England Working Group Report recommendations and support NHS England in meeting the IMMDSR pause conditions within our remit.
- Relevant NICE Interventional Procedures Guidance (IPG) also plays an important role in distilling the evidence of effective practice relating to mesh, and professional societies support individual surgeons to learn and to continually improve their practice.
- Although the MHRA's core role is the regulation of products rather than regulation of clinical practice/treatment pathways or healthcare professionals, we support efforts to enhance clinical practice/training and support of healthcare professionals.
- It is important that all parties in the healthcare system ensure appropriate information is available for healthcare professionals and the public.
- A concerted effort by healthcare system organisations and professional bodies is needed to effectively implement a registry to characterise long-term safety in relation to different surgical procedures using mesh and non-mesh alternatives. This will complement and enhance existing data on outcomes from surgery using mesh. We are fully supportive of the delivery of a registry by DHSC.
- The new Medical Device Regulations which came into force in May 2017 provide more rigorous and specific demands on manufacturers in terms of both pre-market evidence and post-market surveillance to ensure that there is sufficient scrutiny of these devices in both the clinical setting and once they have received a CE mark.

Concluding comment

All parts of the healthcare system need to work effectively together, with a clear and common understanding of patients' concerns, to continue to achieve prompt availability of information and action where appropriate when new evidence about the safety of medicines or medical devices emerges.

MHRA

October 2018

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Introduction and Context

The Medicines and Healthcare products Regulatory Agency (MHRA) is committed to working with the Independent Medicines and Medical Devices Safety Review to improve the healthcare system's ability to respond where concerns have been raised about the safety of particular clinical interventions.

The MHRA agrees that it is important to learn from how the three safety issues in question have been handled, including how to better ensure the patient voice is carefully heard and patients' concerns addressed. We have endeavoured to provide comprehensive answers to each question. We have referenced some other documents in our response which are included separately or can be accessed via hyperlinks.

The Framework Agreement 2016 between the Agency and the Department of Health and Social Care (then the Department of Health) provides important context for this response. This Agreement defines the critical elements of the relationship between the Department and the Agency and sets out the Agency's statutory and non-statutory functions and the legal frameworks in which we operate. The Agency provides the executive function of the UK Licensing Authority for human medicines, a role discharged by the Secretary of State for Health and Social Care on behalf of all interested UK Ministers and is also the Competent Authority for the regulation of medical devices. It also explains the accountabilities and the roles and responsibilities as well as a giving an overview of the Agency's relations with the Department's wider network.

In addition, the Secretary of State, as Licensing Authority, is advised by independent expert scientific committees, for which the Agency provides the secretariat function. The Commission on Human Medicines (CHM) is a statutory committee, established in 2005 from predecessors, which advises Ministers on the safety, efficacy and quality of medicinal products. The Devices Expert Advisory Committee (DEAC) provides independent expert advice on a wide range of aspects relating to medical devices.

A second document of relevance to this response is the Agency's Triennial Review Report July 2015. The aim of the Triennial Review was to test the continuing need for the Agency, both in terms of the functions it performs and the model and approach in which they are delivered, and to consider the Agency's governance, performance and capability.

We recognise the importance of effective collaboration across the healthcare system and in order to protect public health we dedicate resource to optimally maintain our partnerships across the network, the UK and beyond. Our strong links with other healthcare partners enhance the system-wide work to ensure the safety, performance, efficacy and quality of healthcare products used in the UK. We have partnership agreements with principal health sector bodies and hold regular partnership meetings with these and other strategic health sector partners, the Devolved Administrations, and medicines and medical devices industry bodies.

Our current Corporate Plan sets out our aim to enhance our public health through building stronger partnerships, collaboration and engagement, with the intention of enhancing further our contribution to, and engagement with, patient-focused developments. This includes:

- work across the UK health and care system to accelerate access to innovative medicines and medical devices;
- work across the UK health and care system to deepen practical linkages so that as a regulator we can access information about the real-world clinical impact of the products we regulate, and contribute more effectively to informing and influencing clinical practice by providing up to date information on the risks and benefits of the products clinicians use every day; and

- action to improve the way we work with patients, patient groups, clinicians and the wider health and care system to ensure that the risks involved in using some of the products that we regulate can be effectively managed by patients and healthcare professionals, recognising that more needs to be done in this area.

If you consider that further information would be useful, or if you have queries about our response or attachments, please contact us. We are happy to provide more information on this. Finally, the narrative in Annex A provides additional background and context, in the form of an overview of our roles and responsibilities, to the responses provided to the specific questions asked in the call for evidence.

We look forward to working with the Review to understand how the system as a whole can listen more and be more effective in getting messages through and which is acted upon.

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GENERAL QUESTIONS

1) Please could you provide a timeline outlining your understanding and recognition of risks regarding the interventions covered by this Review. This may include: initial recognition of the risk, dates of consequential and significant research studies, and communication of regulatory and professional guidance to clinicians and patients.

Hormone Pregnancy Tests

Evidence on a possible association between Hormone Pregnancy Tests (HPTs) and adverse pregnancy outcomes has been reviewed on a number of occasions in the UK: by the Committee on Safety of Medicines (CSM) when HPTs were available in the UK; by the MHRA in 2014 in response to a request by Dan Poulter MP, then Parliamentary Under Secretary of State for Health; and by a CHM EWG in 2015-2017 in response to an instruction by George Freeman MP, then Minister for Life Sciences. Most recently, the Brown et al data in zebrafish has been reviewed by a CHM Expert Group of toxicologists and by the EU CHMP. All reviews have been consistent in finding that the available evidence does not support a causal association between HPTs and adverse outcomes of pregnancy.

HPTs were medicines available from the 1950s to 1970s (before the introduction of modern-day medicines regulation) which contained sex steroid hormones, most commonly an estrogen and a progestogen, and were used to diagnose pregnancy or treat a disorder of menstruation called secondary amenorrhoea. In the UK, the most commonly used HPT was Primodos (containing 10mg norethisterone and 0.02mg ethinylestradiol per tablet). Women who thought they were pregnant took one Primodos tablet on each of two consecutive days.

A full timeline regarding investigation of the evidence of possible harm associated with Hormone Pregnancy Tests is set out in the report of the CHM EWG on Hormone Pregnancy Tests, together with all the evidence considered by the Group (which has been reviewed in line with duties under data protection legislation, and common law duty of confidence) is published on the CHM website. In addition to the report this includes the following:

- all annexes referred to in the report, including final copies of all the MHRA assessment reports;
- signed minutes of all the EWG meetings;
- declarations of interests for all EWG participants (page 88 of the signed minutes);
- all documents from the National Archives relating to HPTs, as identified by an independent researcher;
- all animal studies on the components of Primodos conducted by Schering;
- all documents provided by the Chair of the Association for Children Damaged by HPTs from the Landesarchiv berlin (both the original documents in English and German and professional translations of the German documents);
- documents submitted by a variety of stakeholders, including patients, in response to MHRA's call for evidence in June 2015; and
- miscellaneous other evidence gathered and submitted for review.

These documents were carefully reviewed in advance of initial publication and redacted (i) to protect personal data (ii) to exclude confidential information (iii) to exclude information subject to legal professional privilege. If further information is required by the Review about any of the redactions made and/or the rationale for the same, then the MHRA will respond accordingly.

Additional information considered pertinent to this question is highlighted in Annex B along with a simplified chronology of events from 1950 to the present day. This includes milestones of relevance/importance such as: key publications; actions taken by regulators and companies, primarily in the UK but also other countries; important developments in pregnancy testing; major legislative changes; and introduction of key guidance.

We wish to highlight that the ad hoc Expert Working Group established to review the recently published research in zebrafish is completely independent of the Group set up by the CHM in 2015 at the request of Ministers to review all the available evidence on the safety of HPTs.

Valproate

In 1971 the original licence application for sodium valproate in the treatment of epilepsy was submitted to the Department of Health. This application was considered by the CSM and its sub-committees. Valproate was initially restricted to use in hospitals and other centres specialising in the treatment of epilepsy before it was approved for general prescription in 1974. Animal data available at the time of authorisation indicated that sodium valproate was teratogenic and the first datasheet dated 1974 indicated that valproate should only be used to treat women of childbearing age in severe cases or in those resistant to other treatment.

The chronology of events from 1971 to date, is provided in a separate annex (see 'Valproate chronology for Q1.doc') which also provides copies of relevant committee minutes and communication documents. The chronology outlines all of the significant regulatory considerations, communications and updates to the product information relating to this issue. As outlined in the chronology, the possible risk of congenital malformation was recognised from the time of authorisation, based on animal studies. Clear warnings about the risk of birth defects associated with valproate were present in the information for healthcare professionals at the time of licensing. The first data sheet for valproate stated that "*In women of childbearing age, the product should only be used in severe cases or in those resistant to other treatment."* and *"This compound has been shown to be teratogenic in animals. Any benefit which may be expected from its use should be weighed against the hazard suggested by these findings."*

Additional warnings have been updated and communicated on numerous occasions since then in response to new and emerging evidence over time and following extensive scientific reviews. In 1982 the CSM considered a paper on sodium valproate and teratogenicity and advised that there was a need for specific research into anti-epileptics and teratogenicity and that there should be an article issued in to healthcare professionals in the bulletin 'Current Problems in Pharmacovigilance' warning about valproate and birth defects. This was issued in 1983. In 1990 additional information on birth defects, particularly neural tube defects, and recommendations on diagnostic screening were added to the product information. In 1993 an article on the risk of neural tube defects was published in 'Current Problems in Pharmacovigilance'. Patient information leaflets became a legal requirement for all medicines in 1999 and in 2001 warnings in the product information for valproate were expanded to reflect the available evidence on birth defects and to state that women should be informed of the risks and benefits of continuing treatment.

In 2003, following consideration by the CSM working group on paediatric medicines of studies looking at valproate and developmental delay, product information was updated to state that women of childbearing potential should not be started on valproate without specialist neurological advice. Warnings describing the available evidence from epidemiological studies on developmental delay were also added and an article published in Current Problems in Pharmacovigilance.

In 2010 a statement was added to the SPC that use of valproate was associated with a greater risk of certain types of malformation than some other anti-epileptic drugs. A

statement was also added that ‘Autistic spectrum disorders have also been reported in children exposed in utero’ based on case reports and small epidemiological studies.

During 2012 and 2013, MHRA received a number of representations from patient groups and in 2013, INFACT attended a meeting with MHRA to discuss their survey results which raised concerns about the lack of awareness among women of the risks of valproate. Because of the concerns raised by INFACT and other patient groups, and the publication of new data on the long term follow up of children exposed to valproate during pregnancy the MHRA triggered and led the 2014 EU-wide review of valproate and the risk of neurodevelopmental disorders. This resulted in detailed warnings being added to product information about the nature and magnitude of the risk with valproate and coordinated communications were developed and disseminated in close consultation with a wide range of patient and healthcare professional stakeholders. Close monitoring of the impact of the actions following the 2014 review led to a further EU wide review and implementation of a Pregnancy Prevention Programme for valproate in 2018.

Abdominal and vaginal pelvic mesh

A timeline of significant events, regulatory considerations, communications, actions and information is provided in Annex C. It includes work by others where MHRA participated which we feel is relevant. Annex D contains abdominal and vaginal pelvic mesh adverse incident figures and Annex E contains relevant NICE’s Interventional Procedures Guidance.

Our market surveillance role monitors adverse events over time of all medical devices. However, we have started our timeline from 2010 which is when we identified a small (42 adverse reports) but increasing number of reports from women who had suffered adverse events relating to the use of mesh device implants which required further investigation.

Since 2010 we have continued to look at many sources of evidence as part of ongoing market surveillance of mesh to treat prolapse and incontinence. We have taken a number of actions to investigate and address an increase in reporting over time as well as highlighting the issues and working with others to consider their place in appropriate treatment pathways.

We have also engaged with a range of stakeholders involved in this issue, including individual patients and patient groups and have responded to their concerns, providing up-to-date and authoritative information of what we have done and what we are doing to continue to protect them and others who need treatment.

2) Please can you provide a brief summary of how adverse events reports are collected, processed and investigated? How effective do you think this process is in capturing adverse events data? How do you think this could be improved?

The Agency has developed reporting systems designed to monitor, and promptly respond to adverse events in the following areas in accordance with EU and UK law:

- **adverse drug reactions including medication errors** *(UK - The Human Medicines Regulations 2012, SI 2012 No. 1916; EU - (EC) No 726/2004 and Directive 2001/83/EC);*
- **defective medicines** *(UK - The Human Medicines Regulations 2012, SI 2012 No. 1916; EU - (EC) No 726/2004 and Directive 2001/83/EC);*
- **medical device related adverse events** *(EU Directives 90/285/EEC Active Implantable Medical Devices, 93/42/EEC concerning Medical Devices, 98/79/EC concerning In Vitro Diagnostic Medical Devices; UK The Medical Devices Regulations 2002. Statutory Instrument 2002 No. 618.);*
- **adverse reactions and events related to blood and blood components** *(EU Directives - 2002/98/EC and 2004/33/EC; UK Blood Safety and Quality Regulations 2005 SI 2005/50, 2005/1098 and 2006/2013);*
- **non-compliant medical devices** *(EU Directives 90/285/EEC Active Implantable Medical Devices, 93/42/EEC concerning Medical Devices, 98/79/EC concerning In Vitro Diagnostic Medical Devices; UK The Medical Devices Regulations 2002. Statutory Instrument 2002 No. 618.);*
- **fake medicines, medical devices and e-cigarettes; and**
- **whistle-blower reporting systems.**

At a high level, each system incorporates the following common elements:

- On-line reporting systems Safety signal detection systems;
- Access to clinical and other relevant expertise;
- Risk assessment systems; and
- Safety message communication systems.

Each system has been tailored to fulfil the requirements of the respective regulations and help the Agency ensure medicines, medical devices, and blood components for transfusion meet applicable standards of safety, quality and performance.

Our reporting systems lead to advice to inform healthcare professionals and/or the public about the risks and benefits of medicines, medical devices and blood components, with the aim of supporting safer and more effective use.

Medicines

The Yellow Card Scheme is the UK system established in 1964 for collecting and monitoring information on suspected Adverse Drug Reaction (ADR) reports. The Scheme is run by the MHRA and the Commission on Human Medicines and encourages voluntary reporting of suspected ADRs by healthcare professionals and patients. The reporting of suspected ADRs

to the Yellow Card Scheme is considered a healthcare professional's responsibility and is included within their professional codes of conduct. There is also a legal obligation for pharmaceutical companies to report serious ADR reports in relation to the products for which they hold marketing authorisations. The Yellow Card Scheme primarily acts as an early warning system for the identification of previously unrecognised suspected adverse reactions and provides valuable information on recognised ADRs, allowing the MHRA to identify and refine the understanding of risk factors that may affect the clinical management of patients.

In order to rapidly identify previously unrecognised concerns about a medicine or changes in the pattern or frequency of a known potential adverse drug reaction which may warrant further action, all reports received by the MHRA are entered onto a database and made available for signal detection. Reports are processed through the system within 15 days to meet legal obligations to notify marketing authorisation holders of serious suspected ADRs to a drug for which they hold a marketing authorisation (or licence). Using statistical software, signal detection is carried out on a weekly basis, for all reports committed to the database the week prior, to identify issues which require further evaluation and to prioritise these according to potential public health impact. The statistical methods used are reviewed on a regular basis to assess their effectiveness[1].

A multidisciplinary team of scientists and healthcare professionals assesses the Yellow Card signals each week alongside additional sources of data including clinical trials, medical literature and information from other international regulators to investigate the possible causal relationship between the suspected medicine or vaccine and the adverse reaction. The MHRA may also ask the marketing authorisation holder for further information and data in relation to a particular drug and event.

If a signal[2] is identified, the safety profile of the medicine is carefully evaluated, and advice sought from the Pharmacovigilance Expert Advisory Group of the Commission on Human Medicines on whether there are implications for the benefit risk balance of the medicine, and if so, the appropriate regulatory action to minimise risk. Regulatory actions can include communication with marketing authorisation holders with a view to implementing risk minimisation measures such as updates to the product information (to add or improve clinical guidance or warnings regarding ADRs), direct communications or the provision of educational materials to healthcare professionals, and changes to the indications or contraindications of the medicine.

Signals can be identified from many different data sources not only through reports received through the Yellow Card Scheme. They can be identified through medical literature, by marketing authorisation holders, through information received from other regulatory authorities, or as direct correspondence and enquiries from healthcare professional or patients. It is important to consider all other available evidence when evaluating a signal regardless of its source.

The value of the Yellow Card Scheme has been demonstrated many times both in identifying potential safety signals and in the use of Yellow Cards as a data source when investigating drug safety issues identified by other methods. Over the past 50 years that the Scheme has been in operation, Yellow Card reporting has helped to identify numerous important safety issues. However, it is important to recognise that all spontaneous reporting systems have limitations. These include underreporting, lack of engagement from some healthcare professionals and often more limited reporting from secondary care, where there has historically been no access to reporting systems at the bedside. Additionally, assignment of causality for spontaneous reports in situations where there is a high background rate of the

[1] Andore G, Juhlin K, Manlik K, Thakrar B, Quarcoo N, Seabroke S, Wisniewski A, Slattery J. Comparison of statistical signal detection methods within and across spontaneous reporting databases. Drug Safety 2015, 38: p577-587.

2 Signal: Information arising from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action [IR Art 19(1)].

event in the exposed population is challenging. Therefore, the MHRA use epidemiological, study, literature and clinical trial data alongside spontaneous reports to address these limitations.

In 2017, the MHRA received its highest number of ADR reports since the scheme was established, with over 44,000 reports received. However; as reporting is voluntary, the MHRA aims to continue to raise awareness of the Yellow Card Scheme, through its Yellow Card Strategy which is designed to continually raise awareness of the Scheme and improve the quality of information they contain. Activities have included display of an information video in GP surgeries, a poster campaign, engaging with health professional bodies and through working with other organisations to develop training information for health professionals. We are also working to increase access to outputs of the scheme, for instance via interactive Drug Analysis Profiles and through the Yellow Card App. More information on activities for 2017 can be found in the Annual Report of the Human Medicines Regulations 2012 Advisory Bodies 2017.The core strands of the Yellow Card Strategy include increasing awareness and accessibility to patients and healthcare professionals, embedding outcomes of actions into the healthcare system and linkage of Yellow Card to other data sources.

To help build awareness of the scheme through healthcare professionals the MHRA works in partnership with a number of organisations. The MHRA funds five regional Yellow Card Centres in Wales, Scotland, the West Midlands, Northern and Yorkshire and the North West regions who are responsible for local outreach activities to engage and promote awareness of the Yellow Card Scheme and associate safety messages. Additionally, the MHRA works with NHS Improvement, particularly in relation to medication errors, to maximise learning and providing guidance to minimise harm relating to these incidents.

In 2014 we established a National Medication Safety Network in England and currently there are over 450 registered Medication Safety Officers (MSOs) tasked with helping to increase reporting and data quality and enable better communication at local and national levels. The network acts as a forum for discussing potential and recognised safety issues, identifying trends and actions to improve the safe use of medicines. Devolved Administrations, CQC and Independent healthcare organisations are also participants of the networks to increase transparency and encourage greater coherent vigilance activities across the UK.

The MHRA commissioned an evaluation of the impact of patient reporting following its implementation which published its recommendations in 2011[3]. The report concluded that patient reporting of suspected ADRs could add value due to the different types of drugs and reactions that were reported by patients. There were a number of recommendations each of which have been implemented by the MHRA where feasible, including changes to reporting forms, evaluation of signal detection approaches and activities to raise awareness of the Yellow Card Scheme.

Another important factor in building awareness of the Scheme is increasing the accessibility of reporting for healthcare professionals and patients. We recently developed, through the EU Strengthening Collaboration in Operating Pharmacovigilance in Europe (SCOPE) Joint Action, led by the MHRA, an e-learning module with Continuing Professional Development (CPD)/Continuing Medical Education (CME) credits available for doctors. MHRA has also developed other e-learning modules to support pharmacists and nurses, however these modules do not encompass all healthcare professionals. Additionally, MHRA has led training for patient organisations through the SCOPE Joint Action to highlight the importance of ADR reporting and engagement with regulators. Further work can be done in this area to improve learning and embed education on the importance of pharmacovigilance into training programmes for all healthcare professionals and patient organisations.

[3] https://www.journalslibrary.nihr.ac.uk/hta/hta15200/#/abstract

We have been working with electronic healthcare record system providers to integrate reporting of Yellow Card into clinical systems since 2009. In 2017 35% of all Yellow Card reports from healthcare professionals were received via clinical systems demonstrating this route forms a valuable component of the Scheme. Given the value integrated reporting adds, we developed the electronic Yellow Card reporting Information Standard in 2013, which forms a core requirement for all GP systems in England as per the GP Systems of Choice requirements. This mandates integration of Yellow Card reporting in primary care systems, however all healthcare systems are recommended to implement the Standard. Although we have successfully integrated Yellow Card reporting into some primary care systems, despite partnership with NHS Digital the largest system supplier, EMIS, has not yet delivered on the requirement. A mechanism to enforce GP system supplier compliance with the GP System of Choice requirement would be a significant step forward.

Integration of reporting in secondary care systems is limited to just one provider currently and therefore this avenue needs to be explored thoroughly to allow greater accessibility of reporting for all healthcare professionals in their work settings. Unlike for primary care systems, there is no core system requirements in secondary care. We have begun work with NHS Digital to utilise Digital Maternity Records a standard currently being implemented into some system providers, although this is not a mandatory component for them to adopt. We have liaised with NHS Digital in order to encourage the implementation of Yellow Card reporting; however, we are reliant on cooperation of suppliers such as EuroKing and K2 in order for the prompt to report to be available more readily for healthcare professionals working within this field.

The MHRA launched the Yellow Card App in 2015 through its leadership the EU Innovative Medicines Initiative (IMI) WEB-RADR project. The platform is now live in 6 countries, with a number of others interesting in adopting the tools over the coming year. The app was developed through user research in multiple countries with the aim of delivering high quality reports through a simplified interface. Studies showed that the app collected data of equivalent quality to traditional mechanisms and is also a powerful tool in providing information to healthcare professionals and patients. The MHRA is currently leading a further IMI project to increase access to the reporting forms and regulatory information through application programming interfaces. These will enable the functionality of the app to be embedded into other systems, such as the recently launched NHS App through engagement with NHS Digital.

Feedback to healthcare professionals and patients is valuable to encourage continued support to the scheme, and enhanced integration of safety messaging into clinical systems is an area that could be optimised to increase the impact of the regulatory system. A pilot is currently underway to feedback to reporters of the Yellow Card Scheme where their reports have contributed to or resulted in regulatory action.

Effectiveness of adverse events reports in respect of medicines

Through the NHS and research organisations, the UK healthcare system generates some of the richest data sets in the world which capture data relevant to the use and safety of medicines. The effective use of other real-world data sources alongside the Yellow Card Scheme is key to improving our wider knowledge and understanding of how patients are treated, their characteristics and other potential confounding factors, and how adverse events manifest at a population-level. This can help us place the very detailed data on individual cases that are reported to the Yellow Card Scheme into the context of the treated population and further explore signals through more robust epidemiological approaches. The MHRA makes particular use of the Clinical Practice Research Datalink (CPRD), which includes a database of longitudinal individual patient level data extracted from GP databases with data on 35 million patient lives including 10 million currently registered patients across the UK, to directly supplement data from the Yellow Card Scheme to strengthen the assessment of signals.

In particular, the MHRA is currently piloting a new software platform designed to rapidly analyse data from the CPRD enabling its routine use as part of the MHRA weekly signal detection process[4]. Initial proof-of-concept work demonstrated the scientific value of the platform in helping place a signal arising from another source, including spontaneous reports, into the context of the UK population and to further explore temporal associations using an unexposed population as a comparator. Work is now ongoing to better understand how this novel approach can routinely support pharmacovigilance with the Agency, where current processes need to be adapted, and how the platform can be enhanced.

As more data sources become linked via the CPRD and as we continue to work with other government bodies and academic groups to gain access to other data sets either routinely generated through the NHS or brought together to support specific research, we will be able to further strengthen our use of data coming from Yellow Cards and increase confidence in the decisions taken with regards to signals by broadening the evidence base in a shorter time frame. The Yellow Card Scheme is able to capture data on a much wider range of medicines and events, including medicines available without prescription and non-serious adverse events for example, than large healthcare databases are able to and for this reason, and the considerably higher level of detail available on specific cases reported via the scheme than recorded elsewhere, we take such a complementary approach, optimising the value of all available and relevant data.

Medical Devices

The Yellow Card Scheme represents one of the Agency's most established contributions to public health. The purpose of the Devices Yellow Card Scheme is to obtain adverse event data, which is used alongside other sources, to enable assessment of potential safety concerns. The Yellow Card Scheme is open to reporting by all; including healthcare professionals within the private healthcare sector and the same professional codes of conduct apply by which we expect reporting of medical device incidents.

- **Yellow Card Promotion activity**

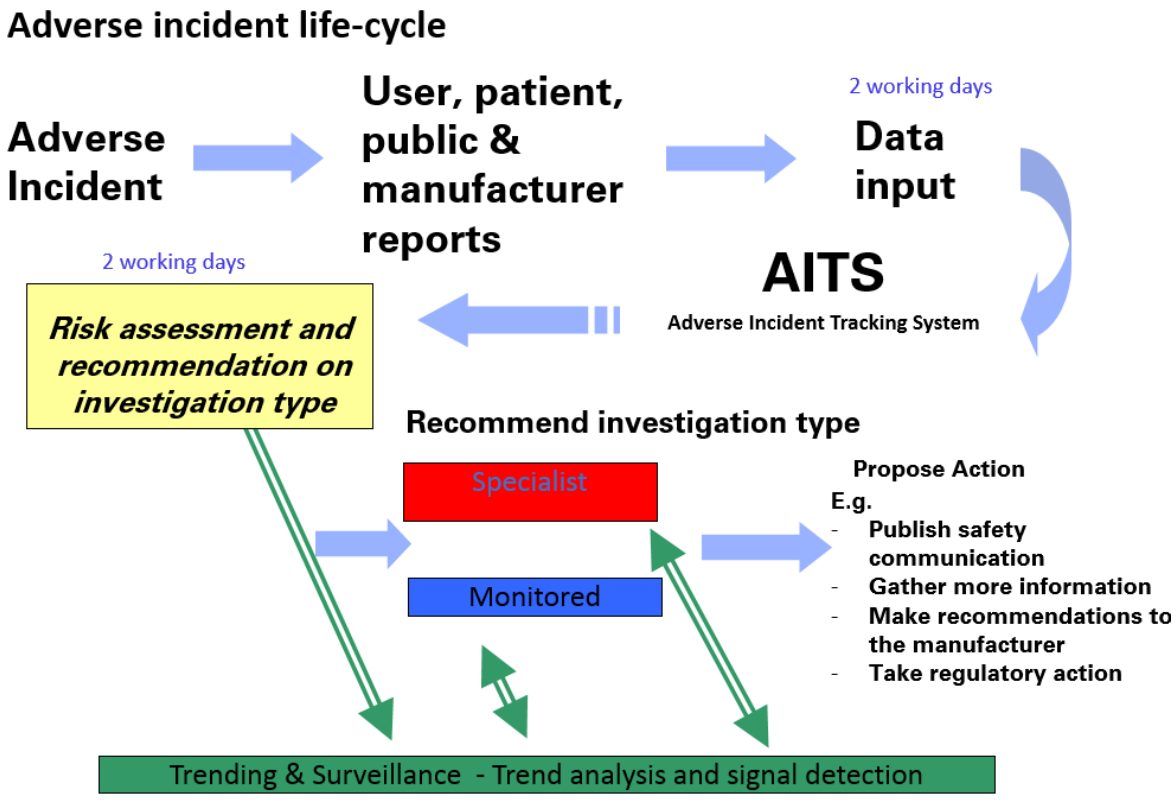
Our strategic approach to devices Yellow Card reporting is supported by the Corporate Plan and Business Plan. 'We will deliver robust proactive surveillance for medicines and medical devices to achieve measurable public health benefit' (Corporate Plan). The business plan outlines specific objectives to ensure that we will develop and implement a Yellow Card Scheme campaign with a particular focus on surgical mesh. Funding has been ear marked to ensure that, in addition to ensuring Yellow Card is referenced in our media materials wherever possible, we also continue to work alongside trading standards; promote the importance of reporting among women who may have experienced complications experience with mesh. We are also increasing our focus on community-based healthcare professionals accessed through professional networks and existing opportunities for messaging.

We are also developing 'train the trainer' style materials, including a range of case studies (not previously identified to support Yellow Card promotion) and physical materials. These have been identified through our proactive engagement with patient groups so that they and any other relevant groups can work independently from the Agency to increase awareness and use of the Yellow Card scheme. By committing our time to creating the collateral we ensure that they are using consistent messaging and appropriate calls to action when encouraging others.

[4] Donegan K, Owen R, Bird H, Burch B, Smith A, Tregunno P. Exploring the potential routine use of electronic healthcare record data to strengthen early signal assessment in UK medicines regulation: Proof-of-concept study. Drug Safety. 2018; 41: 899-910.

- **Medical Devices Safety Officer (MDSO) Network**

In 2014 a National Medical Device safety officer network was established in England in partnership with NHS Improvement and currently there are over 350 Medical Device Safety Officers (MDSOs) tasked with helping to increase levels of reporting and data quality and enable better communication about patient safety at local and national levels. The network acts as a forum for discussing potential and recognised safety issues, identifying trends and actions to improve the safe use of medical devices. This involved actively engaging with Devolved Administrations, Care Quality Commission (CQC) and Independent healthcare organisations who are also guest participants of the networks to increase transparency and encourage greater coherent vigilance activities across the UK.



Above shows an overview of how we collect, process and investigate device related adverse events we receive via the Yellow Card Scheme (also see response to Q3) and those from manufacturers who are legally required to report to us (also see response to Q20).

All medical device adverse incident reports submitted to MHRA are added to our 'Adverse Incident Tracking System' database and are subject to a risk assessment (triage process) carried out by Medical Device Specialists with input from clinical advisers when needed. This process, which takes between three and five days from receipt of a report to triage determination, allows MHRA to focus their specialist resources directly on those issues that present the greatest risk to patient safety, and where their active intervention will help to resolve the problem. As part of this process, all incident reports are recorded, risk assessed and reviewed, but all investigations are supported by systems for identifying, analysing and acting on emerging incident signals, patterns and trends. These systems are regularly refined and updated based on experience.

There are three ways in which MHRA acts on incident reports:

- For incidents where MHRA needs to intervene directly, a medical device specialist (a member of MHRA staff, with a scientific or other relevant qualification/experience),

will be responsible for investigating device adverse incidents in conjunction with the clinical team. These specialist-led investigations may involve contact with the user of the device (via the Medical Device Safety Officer if necessary – see response to Q3), the reporter and the manufacturer. Exceptionally, MHRA may also need to visit the site where the device was used and examine and analyse the device concerned.

- MHRA pursues other incident reports directly with the manufacturer. The manufacturer is legally required to review all incidents (anonymised as appropriate) they receive from MHRA or any other source and consider whether they meet the vigilance reporting criteria and are therefore reportable to MHRA as a requirement of the EU medical device vigilance system – see response to Q8 and Q20). MHRA monitor manufacturers progress to ensure they report back with updates and conclusions, as soon as possible, so that MHRA can assess their findings and any proposed actions.
- Some incident reports may be recorded for trending and surveillance purposes in the MHRA's 'Adverse Incident Tracking System' database. This database covers all incident reports and is central to MHRA's strategy for handling adverse incidents.

Our teams regularly conduct trending which aims to analyse grouped adverse event data by device type, or in greater detail to determine if there is a potential signal for further investigation and will escalate and investigate if necessary to seek resolution as quickly as possible (see response to Q32).

In assessing the weight of evidence behind the adverse event it is possible, but unusual, for one single adverse event to provide sufficient evidence of risk and need to intervene. On most occasions it requires several incidents to be reported to identify a potential device safety signal requiring further risk assessment and consideration of potential action, such as the need for a field safety corrective action by the manufacturer, and/or the issue of a Medical Device Alert.

Also, it is important to know the MHRA monitors relevant evidence from a range of sources as it becomes available, such as scientific papers, correspondence from the public, trends from adverse incidents and/or technical and safety data and does not rely solely on adverse incident data for raising a signal. A signal is an indication from any source which suggests a concern regarding one or multiple medical devices and justifies subsequent action. These different data sources add qualitatively different evidence data, for example, complication rates from hospital episode statistics, inform at device class level, unlike the majority of adverse incident data where the details of the device model are known. Gathering further sources of information helps us better understand the problem.

Furthermore, the continuous analysis of the collated adverse incidents allows MHRA to initiate new investigations where those data have identified emerging safety signals problems and/or unexpected reporting trends and then escalate if necessary to seek a resolution as quickly as possible. This may involve liaising with the manufacture(s) of the device and clinical experts.

Regulatory decisions are made on the totality of the evidence, considering the device, element, clinical practice and treatment pathways and taking appropriate action (see response to Q7).

- **Effectiveness of the process**

The Agency's process in capturing, analysing and acting on adverse events data is effective**.** This is only possible where the data if of sufficient quality for us to draw meaningful conclusions. To facilitate improvements in data quality we are continually working with partners to explore how we can access 'good data' for vigilance purposes from a range of sources.

- **Future Developments**

The Agency has ambitions to unify the medical devices systems and has developed plans for this in a wider reaching operational transformation programme.

MHRA has one of the largest reporting systems in Europe and has a history of promoting, improving and widening the scope of its reporting systems in the light of local and international developments, and it continues to pioneer in this area. Nevertheless, our customer insight work suggests that healthcare workers, carers, and members of the public are confused by the different reporting systems, and often report once having too little time to inform all who ideally need to know for maximising learning.

The Agency is currently pursuing three goals to improve its ability to learn from post market medical device use:

1) that the introduction of a single reporting system, sending information to all relevant bodies in a context sensitive manner would be the single most important reporting development **if designed well**. The Agency is participating expectantly in the patient safety incident management system (DPSIMS) project towards this end. MHRA is a key partner in the development of the Patient Incident Reporting System (PSIMS) which is led by NHS Improvement. Once fully operational this system will replace the National Reporting and Learning System (NRLS) and will simplify reporting for all healthcare professionals and patients. MHRA has systematically increased collaboration with the health care system through the development of Memorandum of Understanding (MOUs) e.g. Care Quality Commission (CQC) and partnership arrangements with the Devolved Administrations to facilitate information sharing.
2) MHRA recognises the importance of well-designed and administered medical device registries to support manufacturers in the fulfilment of their obligations to perform post-market surveillance of medical devices. It is also a valuable and comprehensive source of information for regulators about the safety of new device technologies. Well-functioning and mature registries - such as the National Joint Registry - collect all necessary details of implants and clinical procedures and provide excellent information on both device and the clinician performance, much more comprehensively than a spontaneous reporting system ever could. MHRA is working with other registries in the UK and internationally to enhance their ability to provide good quality information which can be used to underpin regulatory decision making about devices. Examples of this work include the development of guidance on best practice for device registries (such as that already published by the IMDRF) and the definition of internationally accepted registry datasets (e.g. for breast implants) to allow the aggregation of information from multiple national registries. Also see response to Q23)
3) Wider use of real-world data is a better and cheaper long-term solution, which could ultimately supersede the need for running expensive registries. The ability to use data captured in healthcare records about medical devices and medicines, correlated with pseudonymised patients' histories from healthcare records and registries etc, potentially provides a wider and more versatile dataset for analysis and even better learning. For example, we are currently gaining an understanding of the value of CPRD data for supporting medical device post-market vigilance. Clinical Practice Research Datalink (CPRD) linked data is anonymised primary care patient data that can be individually linked to secondary care and other health and area-based datasets. This linkage enables CPRD to provide a fuller picture of the patient care record to support vital public health research, informing advances in patient safety and delivery of care (see response to Q1 timeline).

3) How does the MHRA proactively monitor patient safety concerns, e.g. trend analysis in adverse event reporting, use of social media? How does the MHRA interact with the private healthcare sector in this regard?

Medicines

The Agency proactively monitors patient safety concerns via the Yellow Card scheme, other real-world healthcare data sources, routinely screening scientific and medical publications, monitoring public debate in the media, and the concerns raised by patients and healthcare professionals either directly or via Parliament.

The Yellow Card Scheme acts as a trigger to identify potential safety concerns and provides data, alongside other sources, to enable assessment of these safety concerns. The overall aim of the MHRA is to proactively monitor all data sources for emerging evidence of hazard in as close to real-time as possible. Reports coming via Yellow Cards form part of this but the MHRA also surveys literature published in peer-reviewed journals, routinely monitors all safety data related to each medicinal product through Periodic Safety Update Reports and considers enquiries that come directly into the Agency from patients and their healthcare professionals.

Yellow Card data are reviewed on a weekly basis using statistical methods to determine if we are seeing disproportionately more cases than we would expect for a particular medicine or vaccine and adverse reaction against all other reports on our database. The methods used within the disproportionality analyses are supported by considerable research[5], tailored specifically to the MHRA Yellow Card database, and are used widely for the interrogation of such data sources by other international medicines regulators, marketing authorisation holders, and the WHO. Alongside this statistical approach we also review each week all suspected ADRs resulting in a fatal outcome, and ADRs occurring in a child, during pregnancy or related to any of a list of specific medical terms of interest.

As the Yellow Card Scheme is a 'passive' surveillance scheme we can supplement this by generating supporting evidence using other data sources such as electronic health records, for example the CPRD, which are not reliant on voluntary reporting.

CPRD and other real-world data are used widely to support proactive vigilance for newly introduced vaccines by placing reports coming in through the Yellow Card scheme and reported in the media, into the context of the vaccinated population and the underlying background risk of the adverse event in the exposed population in the absence of vaccination on a weekly basis. This strengthens the assessment of case reports and facilitates both the timely identification of safety concerns and active generation of data on vaccine safety to support a vaccine programme that could be negatively impacted by single reports of events occurring in temporal association with vaccination, but which prove to be unrelated. As the size of the vaccinated population increases we can then use such data sources to conduct larger more robust epidemiological studies designed to further characterise or rule out a risk. A paper published on the HPV vaccine and fatigue syndromes clearly illustrates how the MHRA proactively make use of real-world data to strengthen early signal detection and generate more robust evidence where needed[6].

There is also a wider role for real-world data in routinely supporting a proactive approach to monitoring potential safety concerns for medicines other than vaccines. Routine access to such data from the CPRD is being explored in part through the pilot of a new software

[5] Wisniewski A, Bate A, Bousquet C et al. on behalf of the IMI PROTECT consortium. Good Signal Detection Practices: Evidence from IMI PROTECT. Drug Safety, 2016; 39: p469-490.

[6] Donegan K, Beau-Lejdstrom R, King B, Seabroke S, Thomson A, Bryan P. Bivalent human papillomavirus vaccine and the risk of fatigue syndromes in girls in the UK. Vaccine. 2013; 31: 4961-7.

platform as discussed previously while the MHRA also continues to generate evidence through the conduct of larger more robust epidemiological studies where needed. Real-world data can also enable us to monitor the effectiveness of risk minimisation measures, actively identifying where safety concerns remain and measures need to be strengthened or refined or where inadvertent changes have resulted from regulatory action.

As the data captured or linked within the CPRD increases in volume and quality the MHRA is making more and more use of it and are working with CPRD to increase the strength of the data for conducting pharmacoepidemiology research, undertaking research into how it can be more effectively used to support timely and robust regulatory decision-making, and developing strategies for further proactive monitoring of safety concerns and the effectiveness of risk minimisation to build upon experience. However, while data captured through the NHS are increasing in volume and quality there remains a paucity of observational data accessible from private healthcare and the impact of this needs to be considered when interpreting the data related to a specific issue.

The MHRA has considered the utility of social media data for pharmacovigilance as part of an EU research project, the Innovative Medicines Initiative WEB-RADR project. We led the international consortium which undertook scientific research into the utility of social media data for signal detection with Liverpool University and the WHO Monitoring Centre in Uppsala, Sweden. This research showed that broad-based analysis of social media does not currently result in improvements to signal detection, but targeted approaches for identification of specific issues, such as patterns of abuse and misuse may be appropriate in some situations. The project also undertook research on the legality and ethics of direct communication with social media users by regulatory authorities and the pharmaceutical industry. In summary, analysis of the EU data protection framework, literature and consultation with lawyers, medical ethicists, patients and healthcare professionals concluded that discussion through these platforms should only occur when initiated by the patient/user. Outputs of the project are available through this link. Therefore, the MHRA does not routinely screen social media for patient safety concerns.

The MHRA does use social media as part of its Yellow Card Strategy to raise awareness and increase reporting to the Scheme. In November 2016 we led an EU-wide ADR awareness week campaign. The campaign was the first of its kind using social media through the Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) European Commission Joint Action project which was led by MHRA. Building on its success, in November 2017 in collaboration with WHO Monitoring Centre in Uppsala, we led a second social media ADR awareness week campaign. The 2017 campaign reached nearly 2.3 million people involving 23 medicines regulators, of which 8 were outside EU. In the UK, a month after the 2017 campaign there was an increase of 16% in suspected ADR reports received directly from healthcare professionals and members of the public compared to the same period the year before. A third ADR awareness week campaign on social media is being planned for 19-23 November 2018. This year's campaign has a focus on 'reporting side effects helps the safe use of medicines for babies, children and pregnant women.'

MHRA Interactions with private healthcare sector

As the Yellow Card Scheme is open to reporting by all, this includes healthcare professionals within the private healthcare sector. The same professional responsibility in relation to reporting of suspected ADRs apply to healthcare professionals in the private sector as to those in the NHS. We accept that routine interaction with the private sector remains a challenge. At present we take ad hoc situation-specific approaches to targeting safety messages to private health care for example care homes in relation to use of antipsychotics in dementia; hair loss clinical for finasteride and suicidal behaviour; cosmetic clinics for Botox and spread reactions and travel clinicals for safety information about Yellow fever vaccine and mefloquine.

Medical Devices

The purpose of the Yellow Card Scheme is to obtain adverse event data, which is used alongside other sources, to enable assessment of potential safety concerns. The Yellow Card Scheme is open to reporting by all; including healthcare professionals within the private healthcare sector and the same professional codes of conduct apply by which we expect reporting of medical device incidents.

As shown in our response to Q2 on our adverse event process, all medical device adverse incident reports submitted to MHRA are subject to a risk assessment (triage process) carried out by Medical Device Specialists with input from clinical advisers when needed. As part of this process, all incident reports are recorded, risk assessed and reviewed, but investigations are supported by systems for identifying, analysing and acting on emerging incident signals, patterns and trends. These systems are regularly refined and updated based on experience.

Our Medical Device Specialist teams analyse grouped adverse event data by device type, or in greater detail to determine if there is a potential signal for further investigation and will escalate if necessary to seek resolution as quickly as possible.

Medical Device Specialists also respond to significant social media, newspaper and journal articles involving medical device safety issues as part of their trending activities. This continuous analysis of the collated adverse incident and other data by Medical Device Specialists not only gives important background data for triage and investigation processes, but also allows MHRA to initiate new investigations where those data have identified emerging safety signals problems and/or unexpected reporting trends and then escalate if necessary to seek a resolution as quickly as possible.

The MHRA also works in partnership with NHS Improvement with regards to medical devices to maximise learning and providing guidance to minimise harm relating to these incidents. In 2014 a National Medical Device safety network was established in England and currently there are over 350 Medical Device Safety Officers (MDSOs) tasked with helping to increase reporting and data quality and enable better communication at local and national levels. The network acts as a forum for discussing potential and recognised safety issues, identifying trends and actions to improve the safe use of medical devices. This involved actively engaging with Devolved Administrations, Care Quality Commission (CQC) and Independent healthcare organisations who are also guest participants of the networks to increase transparency and encourage greater coherent vigilance activities across the UK.

As the Yellow Card Scheme is a passive surveillance scheme it is important to supplement this with other data sources such as electronic health records, registries, Health Episode Statistics which are not reliant on voluntary reporting. This is something that MHRA routinely does, through analysis of data from the Clinical Practice Research Datalink (CPRD*) for medicines, and MHRA is currently piloting its use for medical devices (see response to Q1 for CPRD study – 2018 ongoing work). A major barrier that we are trying to overcome is the lack of capture of the specific medical device used in the healthcare records. Hence our keen involvement with the Scan4Safety programme, aiming to capture unique device identifiers in the healthcare records. Also see Q2 and Q31 response.

Dr Ian Hudson; Chief Executive of MHRA and Professor Sir Michael Rawlins; Chairman of MHRA have met with a number of professional and clinical bodies to promote reporting to MHRA, including those who do private work as well as NHS work. Our management, specialist and clinical staff and Communications teams also regularly promote Yellow Card reporting in numerous ways, for example, via:

- their regular contact with Royal Colleges and Professional Associations and Societies, including their publications;
- regular promotion of Yellow Card reporting when speaking at conferences;

- Freedom of Information replies, Parliamentary Questions, correspondence with MPs and Members of the Parliament, where appropriate;
- in sister organisation guidance e.g. NICE Interventional Procedures Guidance (IPG) where appropriate, e.g. For IPGs for procedures which us mesh (see Annex E); and
- in written journal articles.

4) What proportion of adverse events do you believe are reported through the Yellow Card system? How many duplicate reports are made?

Medicines

Our understanding is that a variable proportion of adverse events are reported to us and the MHRA continually strives to keep underreporting particularly of serious suspected ADRs to a minimum level. It has been estimated that 10% of serious ADRs and between 2-4% non-serious ADRs are reported[7],[8] and that serious reactions are five times more likely to be reported than non-serious reactions[9]. The level of underreporting of ADRs to different medicines is variable and dependent on a number of factors such as seriousness of reactions, their ease of recognition, extent of use of a particular drug and promotion and publicity about a drug. Underreporting is a constant concern and we strive at all times to keep the importance of reporting suspected adverse drug reactions particularly at the front of healthcare professionals' minds.

All spontaneous ADR reporting systems worldwide, like the Yellow Card Scheme, are known to be subject to under-reporting. Underreporting of ADRs is thought to occur less frequently with serious and unlabelled reactions (those reactions which are not yet on the product information). In the example of the rare adverse reaction of fibrosing colonopathy associated with high strength pancreatic enzymes in children with cystic fibrosis we understand that all of the cases to occur in the UK were reported to us. This means that under-reporting in the Yellow Card Scheme is less likely to detract from the ability of our signal generation system to identify new and important drug safety hazards. The disproportionality statistical analyses which we use to routinely scan the whole Yellow Card database are purposefully designed to minimise the impact of under-reporting by comparing between drugs rather than with unexposed patients. Further, the MHRA can also apply additional sensitivity analyses into its statistical evaluation of a potential safety concern which takes account of a range of levels of possible reporting.

Surveys of attitudes to reporting of ADRs suggest that lack of time, and uncertainty as to whether the reaction was caused by a drug, are among the most common factors in deterring reporting. To try and address these factors our Yellow Card strategy has a strong focus on making it easy for clinicians to report. We have been working with IT providers to integrate Yellow Card reporting directly within clinician's software; this makes it quicker and simpler for healthcare professionals to complete and send a Yellow Card because much of the information needed can be automatically populated from patient records. We have to date integrated electronic Yellow Card reporting into two GP systems as well as three hospital-based systems. As a result, from clinical systems over 37,700 suspected ADRs reports have been submitted to the MHRA between 2010 and the end of August 2018.

To improve awareness and use of the Yellow Card Scheme by health professionals, we regularly engage with Royal Colleges, healthcare professional bodies, patient support organisations and charities to disseminate key messages about reporting. Other initiatives include development of education modules for healthcare professionals with CPD credits available.

In addition to this, we work with our five Yellow Card Centres across the UK that are mainly based in teaching hospitals and academic settings to educate patients and healthcare professionals locally. Several online educational modules have also been developed to

[7] Reporting adverse drug reactions: A guide for healthcare professionals. May 2006. BMA Board of Science.
[8] Rawlins M (1994) Pharmacovigilance: paradise lost, regained or postponed? Journal of the Royal College of Physicians of London 29:1
[9] Heeley E, Riley J, Layton D, Wilton LV, Shakir SAW (2001) Prescription-event monitoring and reporting of adverse drug reactions. *The Lancet* **358**: 1872-73.

support healthcare professionals to increase their understanding about the importance of suspected ADR reporting and their vital contribution to improving patient safety.

Level of duplicate ADR reports

We routinely identify between 600 and 800 duplicate reports per year, which are merged into a single active record. Approximately 80% of these are related to submissions from Marketing Authorisation Holders, with the remainder where multiple healthcare professional or patient reporters have completed a report concerning the same incident. We have automated and manual detection procedures in place and upon identification these duplicate reports will be merged into one case on our database.

Due to the high volume of ADR reports we receive we are continuously looking at ways to improve our procedures and have led research as part of the Innovative Medicines Initiative PROTECT project[10] to identify the best methods available for duplicate detection[11]. As a result of this we implemented a new method of probabilistic record matching within our database which has achieved good predictive value for identifying duplicate reports. We believe that our duplicate detection procedures are robust, and duplicates have not resulted in identification of false signals in our signal detection activities, and we therefore would not want to discourage reporting because of the possibility of duplicate reports being received.

Medical Devices

Academic research into patient safety incidents reported to official reporting systems compared to those identified by various other means is reported to range from 1% and 50% depending on definition and method.

The Poly Implant Prothèse (PIP) breast implant investigations led by Sir Bruce Keogh and supported by MHRA, included a retrospective collection of the clinical findings at explant, this revealed that 1 in 6 of implant ruptures were reported to MHRA's reporting systems (Paragraph 23, Page 11). We have not done any further studies in the medical device area.As mentioned in our response to Q3, it is important we supplement this with other data sources such as electronic health records, registries, Health Episode Statistics which are not reliant on voluntary reporting.

Also, the MHRA monitors relevant evidence from a range of sources as it becomes available, such as scientific papers, correspondence from the public, trends from adverse incidents and/or technical and safety data and does not rely solely on adverse incident data for raising a signal for further investigation. These different data sources add qualitatively different evidence data, for example, complication rates from hospital episode statistics, inform at device class level, unlike the majority of adverse incident data where the details of the device model are known. Gathering further sources of information helps us better understand the problem.

Furthermore, the continuous analysis of the collated adverse incident allows MHRA to initiate new investigations where those data have identified emerging safety signals problems and/or unexpected reporting trends and then escalate if necessary to seek a resolution as quickly as possible.

On average, duplicate reports account for 3% of the total number of adverse incident reports we receive yearly. Where possible, multiple reports for the same event are linked, however as reporters are not required to complete all fields, we cannot always be sure enough to link every duplicate.

[10] http://www.imi-protect.eu/

[11] Tregunno P, Bech Fink D, Fernandez-Fernandez C, Lazaro-Bengoa, Norén GN. Performance of probabilistic method to detect duplicate individual case safety reports. *Drug Safety.* 2014; 37(4):249-258

5) How do you facilitate signal detection by sharing information from international pharmacovigilance systems?

Medicines

We facilitate rapid signal detection by sharing information from international pharmacovigilance systems through three main approaches; integration with the EU system, which requires and facilitates collaborative assessment and data sharing across the EU network, participation in broader international signal exchange programmes and through memoranda of understanding with individual international regulators.

In addition to comprehensive review of our own database, we assess ADR reports in the form of electronic Reaction Monitoring Reports (eRMRs) from the Eudravigilance database to identify signals of concern. The Eudravigilance database is large and contains worldwide reports of suspected adverse reactions to medicines that are authorized or being studied in clinical trials in the European Economic Area. Each National Competent Authority and the EMA has specific substances assigned for which signal detection is required. eRMRs are produced bi-monthly for additional monitoring medicines and monthly for established medicines. Although eRMRs are reviewed collaboratively across the EU network (with the MHRA currently responsible for assessing 139 substances) we have access to reports for all substances should we identify an issue of concern.

We raise potential signals at EU level via the European Pharmacovigilance Issues Tracking Tool (EPITT) which is a database developed by the EMA to promote communications and tracking of pharmacovigilance and risk management issues across Europe. All relevant information on a particular safety issue, whether the signal is confirmed, or refuted can be found here. All confirmed signals are discussed at the Pharmacovigilance Risk Assessment Committee (PRAC) for which each member state has delegates. We have raised 56 signals in the EU system between 2013 and the end of July 2018, 41 of which were confirmed and discussed at the Pharmacovigilance Risk Assessment Committee. PRAC is responsible for providing recommendations on confirmed signals and decides on any actions to be taken throughout the EU.

In addition, the MHRA has access to the WHO VigiBase database, which is another global dataset which can be used to validate signals where there is limited UK/ EU data on a product. The MHRA has strong international relations, include memorandums of understanding with 21 other countries to facilitate exchange of safety data where appropriate. The MHRA is also part of the International Post-Marketing Surveillance (IPMS) group which involves regulatory authorities from the US, Canada, Australia, New Zealand, Singapore and Switzerland. This group facilitates the exchange of information about the safety of marketed drug products. The MHRA is able to influence signal detection in international countries as well as gain more knowledge through their signal detection activities in return. This exchange of information plays a vital role in our responsibilities for signal detection in the wider pharmacovigilance network.

Medical Devices

The current European databank for medical devices (Eudamed) captures national competent authority (CA) reports of manufacturer's field safety corrective actions (recall a product, amend the instructions for use, or warn of safety issues for example), or CA actions to protect public health. It does not capture all adverse incidents reported in individual countries. MHRA led attempts to create a single centralised EU repository for adverse incidents when EU medical device regulation was under the arm of DG-SANCO. However, with the move to DG-Enterprise this work was refocussed onto developing a much more comprehensive Eudamed MDR databank in the support of the new EU Medical Device

Regulations and EU In Vitro Diagnostics Regulations which will apply in full in 2020 and 2022 respectively.

MHRA, in response to the PIP Breast implant fraud, successfully proposed the introduction of a monthly EU vigilance teleconference with EU member states. Issues causing EU member states a concern can now be discussed and adverse incident numbers pulled together from across all EU Member States, this supports discussion about manufacturers planned actions in an EU forum (see response to Q1 timeline for examples of this in practice). A vigilance enquiry form can be used to gather experience in other EU member states. There is also a National Competent Authority Report (NCAR) exchange with International Medical Device Regulators Forum (IMDRF) (members such as the USA, Canada and Australia) which is used for the most serious risks. In addition, there is a separate form for updating members states about manufacturer compliance issues.

MHRA has in parallel dedicated significant resource into the development of the Eudamed MDR databank and is represented on all its working groups. This database will for the first-time mandate registration of all medical devices sold on the EU market, the capture of Unique Device Identifiers (UDI) for all medical devices, and the central capture of all EU medical device adverse event reports in accordance with new regulations which will apply in full for medical devices in May 2020, and in May 2022 for In Vitro Diagnostics (IVDs).

The capture of Unique Device Identifiers (UDI) in the supply chain, combined with IMDRF terminologies for categorising adverse event reporting (see Q6 for full details) is expected to significantly improve the current knowledge and analysis capability in this area. This, in turn, will facilitate signal detection with a vastly widened and improved dataset.

6) Is there a way to standardise adverse event reporting to allow more comparisons across different studies?

Medicines

Standardisation of adverse event reporting is a fundamental principle underpinning more effective data integration and speedier signal identification. Reporting of suspected adverse drug reaction reports to Regulators follows an international standard specified by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). This standard is used to harmonize and define the data elements for the transmission of individual reports regardless of the source or destination and has been in place since 2005.

The ICH's Medical Dictionary for Regulatory Activities (MedDRA) which we originally developed is used to code all adverse reactions within reports submitted through the Yellow Card Scheme. The MHRA also has a drugs dictionary to which all ADR reports are mapped to ensure information can be aggregated and enable comparisons at different levels (e.g. substance, formulation or product) for signal detection activities. These methods of data capture allow for consistency across all reports submitted, permitting signal detection across many different sources of information and the conduct of complex queries in the database.

Electronic healthcare record systems including primary care services and secondary care systems generally use other medical and drug dictionaries such as SNOMED CT and DM+D. To address this issue, we have completed initial mappings of these two terminologies to MHRA terminologies. We continue to work with healthcare partners such as Vision, TPP, Cerner and Ulysses, to enable automatic exchange of safety data with healthcare systems. We have also supported work within the European Medicines Agency to understand how a common data model, designed to facilitate multi-database research and hence enabling more rapid and robust evidence generation, could be implemented in Europe[12], and will support the CPRD in their implementation of such a model to ensure that it is best placed to enhance UK and global pharmacovigilance.

These differences are relevant to ongoing research the MHRA is conducting to establish the utility of the CPRD to strengthen signals at a very early stage in their assessment process which, as previously highlighted, is an important step in increasing the effective use of other data sources for supporting the assessment of data captured via the Yellow Card Scheme. Initial proof-of-concept work explored the potential use of a software platform specifically designed to provide immediate access to analyses using the primary care data captured within the CPRD and designed to help place a signal arising from another source, including spontaneous reports, into the context of the treatment and UK population and to further explore temporal associations using an unexposed population as a comparator[13]. This pilot has now been extended for a year to better understand how this novel approach can routinely support pharmacovigilance with the Agency and where things need to be adapted. Future work on this approach will potentially extend the resource to other data sets and will also address the issues raised by the different coding systems used for recording events in the different data sources through the use of mappings to ensure consistency between event identification.

[12] https://www.ema.europa.eu/documents/report/common-data-model-europe-why-which-how-workshop-report_en.pdf

[13] Donegan K, Owen R, Bird H, Burch B, Smith A, Tregunno P. Exploring the potential routine use of electronic healthcare record data to strengthen early signal assessment in UK medicines regulation: Proof-of-concept study. Drug Safety. 2018; 41: 899-910.

Medical Devices

Yes, there are ways to standardise adverse event reporting to allow more comparisons across different studies. With medical devices we have been pursuing three important strands of work with our national and international partners to put building blocks in place to deliver this:

1. The development of a new Medical Devices Regulation-ready manufacturer incident reporting form, which will capture trends within each individual incident report, utilising new International Medical Device Regulators Forum (IMDRF) Adverse Event terminology to define and report on similar incidents occurring in the EU country the incident occurred, in the entire EU, and world-wide. So, each individual report will itself be a rich data source. We anticipate this form will be finalised in December 2018 and brought into use across Europe in December 2019, and earlier on a voluntary basis. Once finalised this new report from will have effectively created a new data standard for European manufacturer reporting. Also see response to Q30.
2. MHRA plan to strip inappropriate fields out of this standard to create a new NHS standard for medical device reporting for use in healthcare systems such as Local Risk Management Systems (LRMS) EMIS, DPSIMS, Registries and similar, to facilitate integrated reporting. Also see response to Q30.
3. Working with Scan4Safety and medical device registries to encourage the capture of Unique Device Identifiers (UDI-Device Identifier and UDI-Production Identifier), and international adverse event terminology where appropriate within each relevant clinical database and within the electronic patient records. Also see response to Q31.

This strategy would allow the MHRA Regulator to work with Clinical Practice Research Datalink (CPRD – see response to Q3) and NHS Digital etc. to use these datapools, now populated with rich device data, to facilitate, via linked pseudonymised patient identifiers, comparisons across multiple databases and registries to support safety studies and learning and use it as comparator for our trends in reported adverse incidents. As noted above these types of studies are already possible for medicines, where the medicine used is routinely captured within the healthcare record.

It is however not within MHRA's gift to mandate this. It will require significant partnership working and an expansion of the Scan4Safety initiative across the UK healthcare economy.

7) How does the MHRA discharge its responsibility for patient safety with regard to responding to adverse events and harm reduction?

Medicines

To discharge its responsibility for patient safety with regard to responding to adverse events and harm reduction, the role and responsibilities of the Agency are as set out in the Human Medicines Regulations 2012. These reflect key new responsibilities that were given to the regulator as a result of the European Commission's review of the operation of pharmacovigilance in Europe and the revision of the EU legislation. The EU system of pharmacovigilance and its regulatory basis is outlined in detail in Mann's Pharmacovigilance, 3rd Edition[14].

The purpose of both the UK and EU legislation is timely action in relation to emerging safety concerns and clarity over roles and responsibilities for regulators and industry with regards to pharmacovigilance activities. This is co-ordinated at EU level through the Pharmacovigilance Risk Assessment Committee (PRAC) whose roles include signal detection, conducting safety referrals (Europe wide risk:benefit reviews driven by safety concerns), evaluation of Periodic Safety Update Reports which companies are required to submit and Risk Management Plans (RMPs), which are agreed at the time of licensing, and consideration of the effectiveness of risk minimisation measures. Member States, including UK, are represented by delegates to PRAC who also lead key areas of assessment work either through their responsibilities as reference member state for a product or Rapporteur for a centrally authorised product or through appointment by PRAC. The scientific assessment work is carried out by staff of the appointed leading authority, comprising teams of scientists, healthcare professionals and biostatisticians.

The MHRA operates according to the Good Vigilance Practice (GVP) guidance published by the European Medicines Agency in accordance with the Regulation and Directives. The GVP module on pharmacovigilance of medicines in pregnancy is currently in preparation and MHRA is actively participating in the EMA drafting group.

Within the MHRA, the Vigilance and Risk Management of Medicines (VRMM) Division is responsible for the operation of the pharmacovigilance system including monitoring the safety of medicines after licensing and taking action to protect public health in response to new information which impacts on the balance of risks and benefits of a medicine. The VRMM Division consists of multidisciplinary teams of 130 scientists and healthcare professionals who operate the pharmacovigilance system comprising the detection and evaluation of signals; risk assessments; assessment of Periodic Safety Update Reports, safety variations and risk management plans. The assessment function is organised in therapeutic teams, with each assessor building expertise in monitoring a portfolio of products and these teams are aligned with the Licensing Division, enabling joint assessment of risk management plans and transfer of knowledge about the risk:benefit profile of a product at the time of licensing.

UK reports received from any source, through the Yellow Card scheme or from manufacturers (currently via an EU collection mechanism 'Eudravigilance') are analysed by a team of scientists, pharmacists and doctors to identify previously unidentified safety issues or an increased frequency of known effects. In addition to these reports, we look at data from a variety of other sources when monitoring medicines, including clinical trials, observational studies, the published scientific literature and information from other regulatory authorities. When the information suggests a new potentially causal association, or a new aspect of a known association, between a drug and the suspected event which requires further verification, it is referred to as a 'signal'.

[14] Mann's Pharmacovigilance, 3rd Edition, ed Andrews E.B. and Moore, N. Wiley & Sons Ltd, Chichester, 2014

Where a signal from any source is considered to require further evaluation, a risk assessment is conducted using all available data sources to establish the size and nature of the risk and the impact on the balance of risks and benefits of the product. Where appropriate the MHRA may conduct epidemiological studies using electronic healthcare record data captured within the Clinical Practice Research Datalink (CPRD) to inform a risk assessment. A range of options for risk minimisation are considered. Actions might include adding the information on the new adverse drug reaction to the existing list of adverse effects of the medicine, restricting the uses or supply of the medicine, to in rare cases, withdrawal of the medicine from the market where risks are considered to outweigh the benefits and no measures are considered sufficient to mitigate the risk. Expert advice will be sought from the CHM and its relevant expert advisory group(s), which includes one on pharmacovigilance, on proposed options for regulatory action. Where action is proposed which will significantly impact clinical practice in the UK, Ministers are asked to decide on the regulatory action on the basis of the advice from the Commission on Human Medicines and the advice and change in regulatory position will be communicated.

The MHRA routinely monitors the implementation of important regulatory changes to see if they have been effective in changing prescribing behaviour or preventing harm. MAHs are also be asked to follow up regulatory changes with further studies on drug utilisation and surveys as appropriate. The MHRA then use the resulting data to consider the need for further regulatory measures if the evidence does not suggest that the action taken has been effective in minimising risks.

Medicines Safety Communications

When action is taken in response to new safety information, there are a number of channels of communication to healthcare professionals and patients. Changes to the Summary of Product Characteristics (SPCs) are reflected in the Patient Information Leaflet (PIL) which is supplied with the medicine. Important warnings may be included on the outer packaging.

MAHs have a responsibility to communicate new information on the risks and benefits of their product through Direct Healthcare Professional Communications (DHPC). These letters, and a detailed plan for distribution, are approved by the regulatory authority. MAHs may be required to provide additional educational or risk minimisation materials (eg patient cards, prescriber checklists or acknowledgment of risk forms) where these are considered appropriate.

Important new information, particularly that requiring changes in prescribing or dispensing behaviour or patient monitoring, is proactively communicated to healthcare professionals through our monthly Drug Safety Update Bulletin. If there is complex information for patients to understand or act upon, a patient information sheet is provided for healthcare professionals to give to patients (for example, a patient information sheet on how to use and dispose of fentanyl patches safely in 2018). Advice is usually sought on the content of these patient sheets from clinical or patient representatives.

Drug Safety Update articles are made publicly available on the MHRA website and through the Yellow Card app. Publication alerts for each monthly Drug Safety Update bulletin are sent to a large list of healthcare professionals and to subscribers. Alerts are also sent to information providers and professional organisations (including pharmacy professional organisations and regulators and relevant Royal Colleges). Information providers who are informed of advice include the National Institute for Health and Care Excellence (NICE), British National Formulary (BNF), and NHS Choices (now known as the NHS website). The Agency has agreed criteria with NICE for their assessment and clinical impact of Drug Safety Updates so that they can be actioned and embedded accordingly across NICE clinical guidance. During the planning and drafting of each article, consideration is given to any charities or patient organisations that will need to be made aware of the advice. Analytics are used to monitor engagement with Drug Safety Update articles and routes are given to allow comments from healthcare professionals back to MHRA.

In the case of urgent safety issues or regulatory actions in need of immediate action or that will affect a large group of patients (for example, suspension of a medicine for safety reason or a new contraindication), MHRA issue alerts through the Central Alerting System. The Central Alerting System (CAS) is a web-based cascading system for issuing patient safety alerts, important public health messages and other safety critical information and guidance to the NHS and others, including independent providers of health and social care. The agency will also communicate alerts to contacts in devolved regions for cascade. Examples of recent alerts have been for Valproate, Esmya, and gadolinium contrast agents. CAS communications are usually supported with a Drug Safety Update.

Medical Devices

MHRA Medical Devices Division contributes positively to patient safety in the health system by:

- Approving clinical investigations for medical devices (if they are carried out in the UK - see MHRA's guidance; 'Notify MHRA about a clinical investigation for a medical device').
- Market surveillance of medical devices. This includes managing the Yellow Card Scheme which collects reports of medical device adverse incidents; defective and counterfeit products across the UK. The Scheme acts primarily as an early warning system alongside other sources of information for the identification of previously unrecognised safety issues and secondly to gain further information about the occurrence of incidents in clinical practice to strengthen the safety profile of devices to protect public health. See below for more information.
- Additional aspects of market surveillance of medical devices include the oversight of UK Notified Bodies to ensure they are meeting the standards required to certify devices for the EU market. More broadly, MHRA has oversight of the regulatory system in the UK which ensures that devices meet appropriate standards of safety and performance; where they are not, there are a range of powers in place to take action including removing devices from the market.

MHRA devices discharges its responsibility for patient safety in responding to adverse events and harm reduction by informing manufacturers of the adverse incident reports we have received via data sources such as Yellow Card scheme. We have operated a reporting system for adverse incidents associated with medical devices since the 1980s which has been open to all to report. A computerised reporting system was introduced in 2001.

The Yellow Card scheme then became the route for healthcare professionals and patients and the public to report adverse incidents with medical devices to MHRA in November 2014. The manufacturer may already be aware of these adverse incidents and they must tell us about certain adverse incident reports or safety issues with medical devices which come to their attention (see response to Q20; Vigilance system).

Furthermore, Field Safety Corrective Actions (FSCA) is an action taken by a manufacturer to reduce a risk of harm associated with the use of a medical device that is already placed on the market. Actions include a recall, change of instructions for use or device modification, and the manufacturer shall report it via a field safety Notice (FSN) to MHRA and send to their customers/users. The manufacturer normally asks for an acknowledgement of their FSN from each customer to ensure they have acted on the advice in their FSN.

Following identification of harm or the potential for harm we will ask manufacturers to investigate safety concerns and work with them, as and when necessary, to bring about effective field safety corrective actions. As a responsible regulator we will, in the first instance work to bring manufactures into compliance. MHRA will monitor the efficacy of the manufacturers corrective actions and ensure that all reasonable efforts have been made to

inform all affected parties. If necessary, we can take regulatory action against manufacturers or remove devices from the market.

Where we have concerns about the safety and performance of medical devices we can and do carry all or a combination of:

- publishing safety advice and advising clinicians on the safer use of medical devices (see devices safety communications below and response to Q10 and 12);
- auditing notified bodies to ensure that they are checking on the manufacturers post market surveillance activities and fulfilling their vigilance requirements;
- enforcing European Directives and potentially using enforcement actions to restrict or prohibit use of devices if appropriate (see response to Q21);
- ensuring root cause adverse events in blood safety and quality are accurately recorded and investigated;
- seeking to minimize harm by producing guidance for manufactures and notified bodies e.g. in relation to the safer design of medical devices (see our human factors guidance where we worked with a range of partners to develop guidance for manufacturers to encourage greater consideration of 'human factors' in the design of their medical devices);
- sharing vigilance information between fellow competent authorities (see response to Q5); and
- work with partners to ensure the effective regulation of new and innovative products and technologies as they become available e.g. Artificial intelligence/software.

We also work with health system partners to promote devices safety more generally, including:

- active participation in the DHSC Scan4Safety Trust pilots (see response to Q31);
- Instigating the development of medical device registries e.g. the National Joint Registry to increase and improve the surveillance of high-risk medical devices;
- Being a key partner with GS1, industry and the healthcare system to increase the use of UDI; and
- Work with manufacturers to increase the use of UDI in field safety notices to facilitate the recall of medical devices when required.

The work of the MHRA Devices Division is carried out in line with the Medical Devices Directive (MDD applies to surgical mesh), Active Implantable Medical Devices (AIMDD) and In Vitro Diagnostics Directive (IVDD). We are currently in the transition period for the new Medical Device Regulations (MDR) and In Vitro Diagnostics Regulations (IVDR) which will apply by 2020 and 2022 respectively. The new Regulations build on the Directives to continue to ensure a consistently high level of health and safety protection. MHRA has a range of statutory powers which can be used if a manufacturer fails to comply (see full response to Q21).

Any decision on regulatory action would take into account the protection of public health and criteria such as causality, detectability and probability of recurrence of the problem, frequency of use of the device, probability of occurrence of direct or indirect harm, the severity of that harm, the clinical benefit of the device, intended and potential users, and population affected.

To note, all further responses refer to the MDD and/or MDR which apply to surgical mesh.

Devices Safety Communications

The Medical Device Directives and the new Medical Device Regulations place the onus on manufacturers to maintain a customer list to enable them to disseminate their Field Safety Notices (FSN) to medical device users when they need to conduct a Field Safety Corrective Action. We publish their FSNs on our website for everyone to see. Anyone can sign up to an alert system to be notified when new safety messages are published. When we have concerns we also use a range of communications mechanisms to alert people to actual and potential safety issues.

A MHRA Medical Device Alert (MDA) is the main route of safety communication to the health service open to MHRA. MDAs are usually triggered if the manufacturer has had a limited response / signed acknowledgement to a FSN from its customers, or when there is an unresolved disagreement regarding the content of their FSN. They are designed to provide additional impetus for action or increase 'reach' to ensure patient safety. However, the MHRA is always very clear that FSNs are safety critical and that healthcare providers should not wait for MDAs or further communication from MHRA before taking appropriate action see our flyer on FSNs.

Nonetheless, a MDA will detail all the necessary actions that a healthcare professional or hospital trust needs to take on receipt. The actions can range from acknowledgement of the receipt of the information to an initiated recall from the manufacturer. Depending on the nature of the MDA clinical advice from the MHRA register of experts will be sought prior to publication to ensure that the advice we are providing is clinically sound.

In some circumstances, MDAs are triggered for other reasons such as to raise awareness of a public health/safety risk affecting a broad type of medical device with no specific manufacturer implicated and to encourage reporting. The MDA may provide guidance on managing such an emerging risk and encourage reporting to the MHRA. MDA information is now also included in Dear Healthcare Professional letters alongside medicines.

Decisions to trigger an MDA is made by a group of medical device specialists and devices clinical team. A Medical Device Specialist who is responsible for the investigation presents their assessment of the data and risk and a recommendation for the Technical Management Group (senior group of staff) who agree to its publication.

MHRA manages t*he Central Alerting System* (CAS), a online cascading system for issuing patient safety alerts, important public health messages and other safety critical information and guidance to the NHS and others, including independent healthcare providers.

Other communications mechanisms include One-Liners, targeted letters to the healthcare sector and the inclusion of devices safety information, alongside medicines, in Dear Healthcare Professional letters. We also take the opportunity to communicate information about safety issues via the Royal Colleges and Professional Bodies, via conferences and events and via articles in journals and publications.

Also see response to Q10 and Q12.

System-wide strategic work on strengthening safety messaging

In 2017, MHRA led a system wide partnership group to explore the improved targeting of safety messages communicated to the NHS. This resulted in a one-day Health Summit for senior NHS leaders in January 2018. The messages from this system-wide engagement included the importance of the health system being able to differentiate between 'mission critical' system-wide alerts and educational and informative safety information. NHS Improvement is leading on the development of criteria for system-wide alerts and MHRA is participating in this work with medicines and devices representation. MHRA is developing a work programme to take forward improving educational and informative messages.

8) Where does the MHRA's responsibilities, including disseminating and responding to adverse event reporting, begin and end vis-à-vis the manufacturers and other public bodies?

Medicines

Before a medicine can be sold, supplied or marketed in the UK, the product must have a marketing authorisation and the terms of that marketing authorisation are described in the product information together with conditions to the marketing authorisation. A marketing authorisation is only granted when the competent authority is confident that the data submitted in the application demonstrate that the product is efficacious, acceptably safe and meets the necessary quality standards and consequently the balance of risks and benefits is considered favourable in line with the terms of the marketing authorisation.

Once a marketing authorisation is granted, the marketing authorisation holder (MAH) for that medicinal product must ensure that the product information relating to the product is kept up to date with current scientific knowledge. The legislation also requires that MAHs ensure that the licensing authority is provided with any new information that may require variation of the terms of the marketing authorisation and any other information relevant to the evaluation of the benefits and risks of the medicinal product. There are also clear requirements that any request from the licensing authority to the MAH(s) for the provision of additional information necessary for the evaluation of the benefits and the risks afforded by a medicinal product is answered fully and promptly. It is an offence for the MAH to fail to comply with these legal requirements and compliance is closely monitored by the MHRA and appropriate action take as necessary.

Directive 2001/83/EC sets out the obligations of both MAHs and national competent authorities (NCAs) such as MHRA with regards to pharmacovigilance. The legislation requires that the MHRA uses its pharmacovigilance system to collect information on the risks of medicinal products, the information shall in particular refer to suspected adverse drug reactions (ADRs) in human beings, arising from use of the medicinal product within the terms of the marketing authorisation as well as from use outside the terms of the marketing authorisation, and to adverse reactions associated with occupational exposure. There are well established procedures and processes in place at the MHRA for the collection of emerging safety information (including reports of suspected ADRs), the screening of these data to identify new or changed risks, the assessment of these risks to determine appropriate risk minimisation measures and what communication to healthcare professionals and the public may be necessary.

Article 102 of Directive 2001/83/EC sets out the specific responsibilities of NCAs more fully and in particular, these are the requirement to:

(a) take all appropriate measures to encourage reporting of suspected ADRs by healthcare professionals and patients;

(b) facilitate patient reporting through the provision of alternative reporting formats in addition to web-based formats;

(c) take all appropriate measures to obtain accurate and verifiable data for the scientific evaluation of reports of suspected ADRs;

(d) ensure that the public is given important information in a timely manner on pharmacovigilance concerns with medicinal products – this should be via publication on the MHRA website and other means as necessary;

(e) ensure there are appropriate methods in place for the follow-up of reports of suspected ADRs and in particular for biological products to ensure that all

appropriate measures are taken to clearly identify (through product name and batch number) any biological products that are the subject of ADR reports; and

(f) take necessary measures to ensure that a MAH who fails to discharge its pharmacovigilance obligations is subject to effective, proportionate and dissuasive penalties.

Article 104 of Directive 2001/83/EC sets out the obligation of MAHs to operate a pharmacovigilance system. In detail the MAH is required to:

a) have permanently and continuously at its disposal an appropriately qualified person responsible for pharmacovigilance (to reside in the EC and be responsible for the establishment and maintenance of the pharmacovigilance system);

b) maintain and make available on request a pharmacovigilance system master file;

c) operate a risk management system for each medicinal product;

d) monitor the outcome of risk minimisation measures which are contained in the risk management plan or which are laid down as conditions or requirements in the marketing authorisation; and

e) update the risk management system and monitor pharmacovigilance data to determine whether there are new or changed risks or whether there are changes to the benefit-risk balance of medicinal products.

Article 107 and Article 107a of the Directive also places responsibilities on the MAHs and NCAs, respectively, in terms of reporting of suspected adverse drug reactions to Eudravigilance (the database maintained by the EMA). MAHs are also required to report to the regulatory authority in the country where the adverse reaction occurred. NCAs are also required to ensure that reports of suspected adverse reactions raising from error associated with the use of a medicinal product that are brought to their attention are made available to any other authorities responsible for patient safety within that Member State.

MAHs are also required to submit Periodic Safety Update Reports for their products to the EMA at a frequency which is determined by EMA, based on the level of knowledge about the product. These reports are evaluated by NCAs and considered at European level by the Pharmacovigilance Risk Assessment Committee to determine whether the data contained within these reports impact on the benefit:risk balance of the product and whether it warrants changes to terms of the marketing authorisation.

MAHs may be required to send Direct Healthcare Professional Communications to inform healthcare professionals about a new safety issue or risk minimisation measure with their product, ordinarily such communications are issued when there is a need to take immediate action or there is a change to current practice in relation to the use of a medicinal product. These letters, and a detailed plan for distribution, are approved by the regulatory authority. A DHPC is usually one of a number of routes used to communicate safety information to healthcare professionals (see answer 7 for other routes for communicating safety information).

Since 2014 the MHRA has had a partnership agreement with NICE and collaboration is through quarterly meetings and ongoing engagement. In relation to safety guidance, we notify NICE of safety related changes to the regulatory position which may impact their guidelines and we aim to work with NICE on implementation of major safety actions which require changes to prescribing practice, the ideal being co-ordinated updating of NICE Guidance and regulatory action. In relation to the use of antidepressants (SSRIs) in children NICE and MHRA communicated the regulatory and guideline changes on the same day.

The agency has representatives on the editorial board of the British National Formulary (BNF) and the BNF for children. The BNF is a biannual paper publication and monthly online

updates providing prescribers, pharmacists and other healthcare professionals with up-to-date information about the use of medicines.

Beyond the statutory powers, which influence the manufacture and supply of medicinal products and devices, the MHRA's role is limited. A major limitation is that the MHRA is generally unable to directly regulate the conduct of prescribers, medical practices and pharmacies. These are the regulatory responsibility of the General Medical Council (GMC), Care Quality Commission (CQC) and General Pharmaceutical Council (GPhC) respectively. The responsibilities of these public bodies include ensuring the protection of patients through the effective regulation of the medical professionals and institutions that patients interact with. In many cases, these responsibilities overlap with the MHRA's. In the Human Medicines Regulations 2012, for example, regulation 323 sets out the ability to respond to certain events as between the MHRA and GPhC, stipulating that the GPhC must continue to enforce regulations relating to the sale and supply of prescription only medicines and medicines not subject to general sale where these relate to registered pharmacies. In some areas, the MHRA on behalf of the Secretary of State can make arrangements for the GPhC to enforce certain provisions, most relevantly, this includes Part 13 of the HMRs relating to packaging and leaflets.

There are mechanisms in place to share information with other government agencies and instigate and support joint enforcement investigations where this is the appropriate and proportionate course of action.

In terms of manufacturers and marketing authorisation holders, there are requirements that operate at all times for identification and response to adverse event reports in respect of medicines and devices. In particular, when a manufacturer becomes aware of an adverse event, or any other issue relevant to safety, it is required to notify the MHRA, which leads to the MHRA considering whether to exercise its relevant regulatory powers and/or working with other regulators to ensure the healthcare system can address the issue as a whole. This can also include the imposition of requirements on the manufacturer themselves. The manufacturer has a role in detecting and investigating adverse events and complying with the regulations.

Medical Devices

Throughout the life-cycle of a medical device it is the responsibility of the manufacturer, together with their notified body (as appropriate), to ensure their medical devices comply with relevant Directives and UK law (Medical Devices Regulations 2002 (SI 2002 No 618, as amended) (MDR 2002), and work as intended.

We as a competent authority have a market surveillance role and we will take action if a manufacturer does not comply with the law (see response to Q7 and Q21).

We do not enforce the legislation over healthcare professionals (that is for the professional bodies that represent them and other regulators such as Care Quality Commission) but we work in partnership with the various governing bodies to ensure the successful operation of the system.

Detailed European Guidance on the various responsibilities for medical devices post market vigilance reporting is contained in the European Commission's guidelines on a medical devices vigilance system.

These guidelines are broad in scope and describe the requirements of the Medical Device Vigilance System as it applies to or involves:

- Manufacturers;
- Competent Authorities (CA) e.g. MHRA;

- the European Commission;
- Notified Bodies (independent / third-party certification organisations to assess whether manufacturers and their medical devices meet the requirements set out in legislation.); and
- Users and others concerned with the continuing safety of medical devices.

The guidelines cover the actions to be taken once the manufacturer or competent authority receives information concerning an incident involving a medical device. Information on incidents which should be reported under the medical device vigilance system may come to the attention of manufacturers via the systematic procedure to review experience gained from devices in the post-production phase, or by other means (see annexes II, IV, V, VI, VII of MDD and annexes III, IV, VI and VII of IVDD – which are all available online).

The term "post-marketing surveillance" as referred to in Annexes 2, 4, 5 in AIMD has the same meaning as the aforementioned "systematic procedure".

The guidelines cover Article 8 (AIMD), Article 10 (MDD) and Article 11 (IVDD) outlining the obligations of Member States upon the receipt of incident reports, from manufacturers or other sources, concerning any medical device.

They also include guidance to Competent Authorities about the issue and receipt of information from National Competent Authorities outside Europe who are involved in the International Medical Device Regulators Forum (IMDRF) exchange programme.

The guidelines are relevant to incidents occurring within the Member States of the

European Economic Area (EEA), Switzerland and Turkey with regard to:

a) devices which carry the CE-mark;

b) devices that do not carry the CE-mark but fall under the directives scope (e.g. custom-made devices);

c) devices that do not carry the CE mark because they were placed on the market before the entry into force of the medical devices directives; and

d) devices that do not carry the CE-mark but where such incidents lead to corrective action(s) relevant to the devices mentioned in a), b) and c).

Devices Safety Communications

Please read in combination with response to Q7 and Q10.

The Medical Device Directives and the new Medical Device Regulations place the onus on manufacturers to maintain a customer list to enable them to disseminate their Field Safety Notices (FSN) to medical device users when they need to conduct a Field Safety Corrective Action to recall a product, amend the instructions for use, or warn of safety issues for example. Medical Device Alerts (MDAs) are usually triggered if the manufacturer has had a limited response / signed acknowledgement to a Field Safety Notice (FSN) from its customers.

A MHRA Medical Device Alert (MDA) is the main route of safety communication to the health service open to MHRA. Other communications mechanisms include One-Liners, targeted letters to the healthcare sector and the inclusion of devices safety information, alongside medicines, in Dear Healthcare Professional letters. We also take the opportunity to communicate information about safety issues via the Royal Colleges and Professional Bodies, via conferences and events and via articles in journals and publications.

9) Do you consider your organisation to be proactive or reactive in regards to learning from adverse events? How do you demonstrate this?

Medicines

In the last decade, MHRA has led internationally to transform pharmacovigilance from a reactive to a proactive regulatory function. In regard to learning from adverse events, the MHRA played an influential role in the development of the 2012 update to European Pharmacovigilance legislation which embedded the concept of proactive pharmacovigilance and monitoring of impact of regulatory action. This was in turn heavily influenced by work MHRA was already doing following the development of our model for excellence in pharmacovigilance published in 2003. The MHRA also had (and continues to have) a lead role in development of the Good Vigilance Practice guidelines.

Driving pharmacovigilance from a reactive to a proactive function has primarily been achieved by the introduction of risk management plans which aim to generate evidence to fill 'knowledge gaps' in safety particularly for new medicines, and also by the introduction of more systematic monitoring of the effectiveness of risk minimisation [15]backed by legal powers. In order to deliver on both these new approaches, we have established a pharmacoepidemiology function within the Vigilance and Risk Management of Medicines Division.

The focus of risk management plans has primarily been on medicines early in the product life-cycle, where signals of potential adverse reactions for medicines are identified but further evidence is required in order to confirm a risk. This particularly applies to potential signals identified during drug development where phase 3 clinical trials were unable to rule out a small risk and further evidence is required, these are flagged as potential risks in the Risk Management Plan. The element within the Risk Management Plan known as the pharmacovigilance plan must then identify how further evidence on these potential adverse events will be generated. Areas of missing information, for example safety in populations not included in pre-licensing clinical trials or where there is inadequate post-licensing experience, but where use is likely, are also proactively identified and evidence gaps addressed in this way.

Until the revised European pharmacovigilance legislation mandated studies of the effectiveness of risk minimisation, our efforts to learn from adverse events were ad hoc. Examples include the study of the effect of the withdrawal of co-proxamol on deaths from drug poisoning[16]; the impact of the national dementia strategy on the prescribing of antispychotics in dementia[17] , the impact of regulatory action on concomitant use of renin angiotensin system inhibitors[18], the effect of the change of paracetamol pack size on poisonings and deaths[19] and the impact of changing the use of N-acetylcysteine in the management of paracetamol overdose[20].

Since the revised EU legislation came into force we have utilised the ability to require Marketing Authorisation Holders to conduct follow-up studies on effectiveness of risk minimisation after major EU safety reviews to evaluate whether the measures have worked

[15] https://www.ema.europa.eu/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-xvi-risk-minimisation-measures-selection-tools_en-3.pdf
[16] Effect of withdrawal of co-proxamol on prescribing and deaths from drug poisoning in England and Wales: time series analysis. Keith Hawton et al BMJ 2009; 338 doi: https://doi.org/10.1136/bmj.b2270 (Published 18 June 2009)
[17] Trends in diagnosis and treatment for people with dementia in the UK from 2005 to 2015: a longitudinal retrospective cohort study Lancet Public Health 2017; 2: e149–56 Published Online February 23, 2017 http://dx.doi.org/10.1016/S2468-2667(17)30031-2
[18] The impact of regulatory action on the co-prescribing of renin–angiotensin system blockers in UK primary care† Pharmacoepidemiology and Drug Safety 2017; 26: 858–862
[19] Hawton K, Bergen H, Sinkin S et al. Long term effect of reduced pack sizes of paracetamol on poisoning deaths and liver transplant activity in England and Wales: interrupted time series analyses. BMJ 2013; 346 doi: https://doi.org/10.1136/bmj.f403 (Published 07 February 2013)
[20] Thompson G, Fatima SB, Shah N, et al. Impact of amending the acetylcysteine Marketing Authorisation on treatment of paracetamol overdose. ISRN Toxicology. 2013; Article ID 494357

to protect patients and the public in the way intended (e.g. Hydroxyethyl starch, domperidone, valproate[21]).

If there is no requirement placed on a marketing authorisation holder to assess the effectiveness of risk minimisation following European review and/or where there is a particular UK public health need for additional or more rapid data, the MHRA will assess the feasibility of using currently available data sources to monitor or measure impact and effectiveness. This results in 2-3 large studies being conducted in-house every year with additional smaller data extracts conducted on an ad hoc basis. MHRA already commits to reviewing all regulatory actions related to risk minimisation for medicines to assess where there is a need to monitor effectiveness and prioritise these for future study and ensure monitoring is undertaken for all European referral procedures where feasible. The MHRA is also developing a strategy for how this work can be improved, building on our experiences with monitoring the changing use of valproate, with consideration of the need for access to new data sources, the methodological approaches that should be used, IT requirements for facilitating more routine monitoring, how it can be supported by building upon relationships with academia, healthcare professional organisations, and the NHS, and how to best ensure evidence feeds back into decision-making in a timely and robust fashion, for example.

As part of our continuous optimisation of our internal and external facing systems the Yellow Card strategy aims to strengthen our ability to detect safety signals in as close to real time as possible. The MHRA has successfully bid to lead European projects designed to increase pharmacovigilance capability (SCOPE Joint Action) and provide tools which are now being widely adopted internationally (IMI WEB-RADR) as described in the response to Question 2. Furthermore we have led and participated in important methodological research in signal detection (via the EU projects IMI PROTECT and IMI ADVANCE).

Our proactive approach to pharmacovigilance has driven research and implementation of many of the strategies described in response to questions elsewhere in this document. For example, introduction of mobile reporting, signal detection activities performed weekly; more frequently than all well recognised international regulators and use of real-world evidence in the CPRD routinely alongside spontaneous reporting data.

Medical Devices

We are proactive and reactive in regard to learning from adverse events in the following ways:

A) Medical Devices Vigilance Systems are both reactive and proactive. Also see response to Q20 and Q21;

B) Liaising with international regulators – monthly teleconference with EU – Silimed response coordinated internationally with teleconferencing;

C) Communicating with the public – guidance for healthcare workers and users of over the counter devices;

D) Improving registries; and

E) Use of real-world data.

We are dependent on reports of adverse incidents with medical devices reaching us. Manufactures are mandated to report to us as part of their vigilance responsibilities as required by the European Medical Devices Directive 93/42/EEC, which was transposed into UK law as the Medical Devices Regulations 2002 (as set out in response to Q1). Other reports from healthcare professional and members of the public are voluntary. Once we are

[21] https://www.ema.europa.eu/medicines/human/referrals/hydroxyethyl-starch-hes-containing-medicinal-products, https://www.ema.europa.eu/medicines/human/referrals/domperidone-containing-medicines, https://www.ema.europa.eu/medicines/human/referrals/valproate-related-substances-0

aware of potential issues with medical devices we are proactive with manufacturers in addressing patient safety concerns via field safety corrective actions. The Poly Implant Prothèse (PIP) implant fraud presented an opportunity for MHRA to review and revise approaches to patient safety and vigilance. Over the last few years we have worked towards being more proactive in seeking adverse incident reports and learning from other competent authorities and professional groups about potential safety issues with medical devices. Please see the full response to Q3 for examples.

As mentioned elsewhere we have also worked in partnership with the NHS Improvement (NHS I) patient safety team to develop a network of Medical Devices Safety Officers (MDSOs). These are situated in NHS trusts and enable us to champion the importance of adverse incident reporting and learning on the ground. The networks resulted from a joint 2014 Patient Safety Alert 'Improving medical device incident reporting and learning', we support the networks through monthly webexes and an annual conference which is held in partnership with Medication Safety Officers (MSO).

At an organisation level we are proactive in learning from experiences of dealing with adverse events and this learning has resulted in numerous changes to our systems and processes. We now place a greater emphasis on engagement with international regulators to share information and ensure that we have mechanisms in place to co-ordinate responses if required. This change resulted from lessons learned in the PIP implant fraud. This approach was particularly useful in response to Silimed. We were able to quickly establish regular teleconferences with international regulators to share information, co-ordinate responses and take timely action.

We reviewed how the regulator receives clinical advice, we commissioned Sir Terence Stephenson to undertake a review and made 12 recommendations for MHRA action. We then reported on our progress against recommendations a year on, although some work remains ongoing and has been incorporated into how the division conducts its 'core business', the paragraphs below summarise actions taken to fulfil Stephenson's recommendations. The Expert clinical advice – MHRA medical devices independent review: report on progress can be found here.

- Recommendation 1: Greater collaboration with healthcare professionals and the healthcare system. This has taken place through the development of the Devices Expert Advisory Committee (DEAC – see response to Q36 on what they do), the register of devices experts (a range of healthcare professionals and scientists who provide us with clinical and technical advice) and greater partnership working with the NHS system such as Care Quality Commission (CQC) and NHS Improvement (NHSI). This is also reflected in the agency corporate plan and business plan.

- Recommendation 6: Build links with Clinical Commissioning Groups (CCGs) and Primary Care - we now have increased capacity within the agency to engage with CCGs, primary care and community health services to increase adverse incident reporting from medical devices. This links with work to improve reporting from healthcare professionals and commissioning user insight work to inform the future strategic direction.

- Recommendation 7: Improving reporting by adopting the Yellow Card Brand and seeking to further enhance and promote this as a reporting route. The number of Yellow Card reports for medical devices has risen year-on-year. We have recently undertaken user insight to inform communications campaigns to promote Yellow Card. This user insight particularly targeted community health care professionals and primary care. We are committed to the development of mobile adverse incident reporting for medical devices.

MHRA is a key partner in the development of the Patient Incident Reporting System (PSIMS) which is led by NHS Improvement. Once fully operational, which we might anticipate will be in 2019/20, this system will replace the National Reporting and Learning System (NRLS) and will simplify reporting for all healthcare professionals. MHRA has systematically increased

collaboration with the system through the development of MOUs e.g. CQC and partnership arrangements with the Devolved Administrations.

The MHRA led system-wide work on improving the impact of safety messaging as part of the agency Patient Safety and Vigilance Strategy. MHRA led a partnership across the healthcare system including PHE, NHSI, NHSE, NHSD, Royal Colleges and Professional bodies. The partnership delivered a 'health summit' in January 2018 for senior leaders in the NHS which identified a strategic direction for improving safety messages. This includes better targeting, a single route of communication, an emphasis on 'mission critical' as well as 'preventative messages which provide information for healthcare professionals and are linked to education and improvement science.

Another example of a proactive approach from MHRA and an attempt to operate 'up-stream' to prevent patient safety incidents occurring as a result of the design of medical devices is our work with stakeholders to develop guidance for manufactures and notified bodies: MHRA guidance; *Human Factors and Usability Engineering – Guidance for Medical Devices Including Drug-device Combination Products for medical devices* published last year sets out to address how environmental and human factors impact the safe use of medical devices.

In recent years, we have taken a more proactive approach in our communication with patients and the public where we have potential safety concerns. This was also a recommendation from the Stephenson review. For example, this link is targeted at patients and healthcare professionals and outlines the actions taken and being taken by MHRA to proactively monitor Breast Implant Associated Anaplastic Large cell Lymphoma (BIAALCL) and gives advice.

Additional examples of a proactive approach is work we have done with patient groups and manufacturers on over-the-counter medical devices. This has involved working with organisations such as Diabetes UK to promote the safer use of blood glucose meters and improve reporting of problems and potential problems. The agency also has a patient group consultative forum which is managed by the Communications Division. Where possible we take advantage of the forum to seek views from patient groups to inform the work we do, for example, there was a recent discussion on Yellow Card at a forum event.

MHRA has also taken a proactive role in the development of registries for high risk devices such as the national joint registry and the breast and cosmetic implant registry which is managed by NHS Digital. We are increasingly using registry data as part of our proactive approach to vigilance. This is only possible where the data if of sufficient quality for us to draw meaningful conclusions. To facilitate improvements in data quality we are continually working with partners to explore how we can access 'good data' for vigilance purposes. Examples of this include partnership with NHSI on the development of the patient safety incident management system (DPSIMS). We are also exploring with MHRA vigilance and risk management in medicines and NHS Digital and NHS England how we can access NHS data-sets for analysis to enable us to detect earlier and better signals. See Q1 timeline for mesh on exploring value of CPRD data.

10) Please can you provide details of your relevant policies and protocols, if any, for ensuring that information relevant to patient safety, and learning from adverse events is disseminated.

Medicines

We maintain a comprehensive set of standard operating procedures that describe the procedures and activities relating to the pharmacovigilance system and operate according to the good pharmacovigilance practice guidance published by the European Medicines Agency in accordance with the Regulation and Directives. These procedures include promoting the safe and effective use of medicines, conducting ongoing vigilance, investigating suspected adverse reactions, applying regulatory measures and providing comprehensive drug safety information to healthcare professionals and to the public. As part of this there are several standard operating procedures for ensuring that information relevant to patient safety and learning from adverse events is disseminated. The following standard operating procedures describe relevant factors such as the urgency of the issue, the nature of the action required and the audience in considering relevant communication tools.

VRMM Major incident identification and management

A possible major safety incident may be identified from within the Division's work, from the marketing authorisation holder, the media, other international regulatory authorities or published literature. This standard operating procedure covers the identification and escalation of potential major incidents relating to drug safety, including interaction with stakeholders to ensure early and effective communication.

Suspension and revocation of national, mutually recognised or decentralised marketing authorisations

Occasionally a risk benefit assessment will lead to the suspension or revocation of a marketing authorisation. This sets out the procedure to follow to escalate any issues that may lead to the suspension or revocation of a marketing authorisation, including seeking expert advice, liaising with the EU network where necessary and informing UK ministers. Early communication with the marketing authorisation is essential to ensure that there is a good understanding of the issues under assessment and the likely timescale of any action. A national communication plan is developed in line with the Standard Operating Procedure on 'Dissemination of complex or significant safety messages for medicines.' In addition, there is a requirement for a post-incident report to consider learning points for VRMM.

Referral procedures for safety reasons

When new hazards arise, which may impact on the benefit risk balance, there is a need to consider initiation of a referral procedure under Article 31 or 107i of Directive 2001/83. This standard operating procedure sets out the procedure to follow to initiate such a safety referral or when a referral procedure for safety reasons is initiated by another member state. The need for press handling and including information on our website are considered, as well as the requirement for a post-incident report.

Central Alerting System: how to send a safety message.

The Central Alerting System is a web-based cascading system to the NHS and others, including independent providers of health and social care. We have a standard operating procedure for using the Central Alerting System where the nature of the safety concern, the risk minimisation measures or the medicinal product(s) affected are such that they either result in significant restrictions to the use of a product or affect a very widely used medicinal product(s).

Dissemination of urgent and complex safety messages for medicines.

The standard operating procedure defines criteria to compile a communication package for complex and usually newly identified risks to ensure that safety communications deliver relevant, clear, accurate and consistent messages and reach the right audiences at the right time for them to take appropriate action.

Production of Drug Safety Update

We have a standard operating procedure in place for the production of Drug Safety Update bulletin every month to promote the rational, safe and effective use of medicines, preventing harm from adverse reactions and contributing to the protection of patient's and public health.

Handling Coroners Regulation 28 reports to Prevent Future Deaths (PFDs)

We have a standard operating procedure in place for handling Coroners Regulation 28 reports to Prevent Future Deaths. This includes the need to consider liaison with organisations across and outside of government. These reports are an important source of pharmacovigilance information and where necessary we have taken action to raise awareness of cases in Drug Safety Update.

Communication of drug safety issues/direct healthcare professional communications

Information is also disseminated by the marketing authorisation holder(s) in line with their legal obligations, in the form of a Direct Healthcare Professional letter. The standard operating procedure considers the content, timing and distribution list for this letter with the marketing authorisation holder. The final copy of the letter is also made available on the MHRA website and a link sent to healthcare professionals as part of Drug Safety Update.

MHRA interactions with the British National Formulary

The British National Formulary is a biannual paper publication and monthly online updates providing prescribers, pharmacists and other healthcare professionals with up-to-date information about the use of medicines. The standard operating procedure is in place to ensure that the British National Formulary is consistent with the regulatory position. This includes responsibilities in relation to interactions such as liaison meetings, Joint Formulary Committee/Paediatric Formulary Committee meetings and to identify areas where updates to the British National Formulary may be warranted.

Medical Devices

Devices main lines of communication are with healthcare professionals rather than directly with members of the public who are users of medical devices. There are exceptions to this when devices that are used by patients are difficult to trace and are widely distributed within the community, for example wheelchairs, blood glucose meters and products that are purchased over the counter from high street pharmacies and supermarkets.

When there is a need to communicate with members of the public directly, Devices works in conjunction with our Communications Division to convey important safety messages. The use of social media, press releases, and radio and television form an important part of this process, as well as engaging with patient groups and/or charities.

As stated in response to Q7 within Devices Safety Communications, the Medical Device Directives and the new Medical Device Regulations place the onus on manufacturers to maintain a customer list to enable them to disseminate their Field Safety Notices (FSN) to medical device users when they need to conduct a Field Safety Corrective Action to recall a product, amend the instructions for use, or warn of safety issues for example. We publish their FSNs on our website for everyone to see. You can also sign up to an alert system to be notified when new safety messages are published.

In this case, MHRA will only publish additional guidance when the manufacturer has failed to communicate effectively with its customers, limited responses (signed acknowledgments) by

its customers to its FSN, or when there is an unresolved disagreement regarding the content of their Field Safety Notice.

Medical Device Alerts (MDAs) drafting, publishing and reviewing and monitoring outcomes

The usual method of communication with healthcare professionals is through the publication of a Medical Device Alert (MDA). These are distributed through the Central Alerting System (CAS) through the Medical Device Safety Officer (MDSO) network within hospital trusts in England (an equivalent network of MDSOs is planned for the Devolved Administrations in Scotland, Northern Ireland and Wales).

In some circumstances, MDAs are triggered for other reasons such as to raise awareness of a public health/safety risk affecting a broad type of medical device with no specific manufacturer implicated. The MDA may provide guidance on managing such an emerging risk and encourage reporting to the MHRA.

Decisions to trigger an MDA is made by a group of medical device specialists and devices clinical team. A Medical Device Specialist who is responsible for the investigation presents their assessment of the data and risk and a recommendation for the Technical Management Group (senior group of staff) who agree to its publication.

There is a consultation process within this procedure and we ask for comments from a range of stakeholders to ensure our message is clear and actionable. These stakeholders can include:

- Devolved Administrations;

- professional bodies and organisations;

- trade associations;

- the reporter(S) of the adverse event that lead to an MDA; and

- a relevant member of Devices Expert Advisory Committee (DEAC) or from our register of experts.

Compliance of the healthcare system with safety alerts issued through the Central Alerting System is monitored during inspections by the Care Quality Commission. We also have our own monitoring system which provides feedback on receipt of the MDA, analysis of the need for action and completion of the required action by the those in receipt of the MDA.

The MHRA therefore has an important role in working with professionals and the public, not only to inform but to also influence their behaviour when using medical devices.

Other Devices Safety Communications:

- Targeted letters: for small numbers of device users who are affected by a safety issue (around 20) an alternative to the MDA is to issue a targeted letter to these users so they are aware of an FSN issued by the manufacturer. These are either sent directly to them or distributed through the MDSOs. This targeted approach reduces the burden on others to act on alerts not relevant to them.

- One Liners production and management: a poster style communication aimed directly at healthcare professionals to address specific issues related to the safe use of medical devices. These are not intended for the public and are normally raised through the MDSO network for onward dissemination. All medical devices can fail but an increasing number of incidents that result in significant morbidity or mortality arise out of user/device interface problems or because of poor practices. The aim of these news sheets is to detail briefly some of these problems to make users more aware of what can go wrong. Some editions focus on a specific device or theme or are of interest to primary care trusts.

- Drafting and publishing a Device Bulletin: Contains guidance and information on medical devices of a more general management interest.

- There is a process in place to enable communication of safety issues to and from the other Competent Authorities in Europe. The National Competent Authority Report is a formal method of alerting other Competent Authorities of a device safety issue when it is known that the affected product is in use in other EU countries.

- MHRA participates in regular teleconferences with the Competent Authorities across the EU. These provide an opportunity to share details of emerging issues with medical devices and attempt to provide a coordinated response across Europe. These teleconferences have proved to be a valuable forum for the exchange of information. Also see response to Q5.

- We also have extensive relationships with clinical professional bodies which are facilitated by the Devices Expert Advisory Committee. Where there are safety issues that can also be disseminated through those channels then these are used. In many cases the risk to patients may be in part the result of clinical practice issues and these channels are used to support messaging. In general, Expert Advisory Committees are used where necessary to support the Agency in the analysis of complex issues and help develop appropriate messaging for the clinical community.

11) Are regulatory decisions made with reference to the data capture of any/ all existing EU registries? If not, why not? Do any of the registries currently in operation meet the standards set by the International Medical Device Regulators Forum. Please highlight those that do. For those that do not are you able to say what are the common missing elements?

Medicines

Patient data captured within any international registry can be considered by the MHRA as part of the evidence base for any regulatory decision related to a medicine. Registries provide important evidence related to the use, safety, and effectiveness of medicines relevant to their regulation particularly for rare diseases. Examples where registries have provided the data on risk for consideration by regulators of action include anti-TNF agents and British Society of Rheumatology Biologics Registry and regulatory action on risk of infection especial TB[22].

Evidence from a registry can be submitted by a Marketing Authorisation Holder in particular for pharmacovigilance studies as part of a risk management plan. The MHRA also have specific links with a number of UK and EU registries and registry networks to facilitate access to any new evidence generated and to advise on regulatory requirements with regards to data quality and completeness. These links include, for example, MHRA representation on specific registry expert advisory groups and established relationships with relevant academic groups.

Any potentially relevant data arising from a registry will be critically appraised to assess its value in contributing towards a particular regulatory decision. The EMA and the European medicines regulatory network have also undertaken work to identify how registries can be improved to optimise their value to providing data for regulatory decision-making and has brought together registries and clinicians within selected clinical areas to address issues of missing and inconsistently recorded data. The EMA patient registries initiative aims to protect public health through the better use of registry data to support benefit risk evaluation. Registries which have been 'qualified' through this initiative include the European Society for Blood and Bone Marrow Transplantation (EBMT) as suitable as a data source for regulatory purposes for CAR-T cell therapies authorised for haematological malignancies; The European Cystic Fibrosis Society Patient Registry and the European Haemophilia Safety Surveillance Registry for Factor VIII products for haemophilia.

Medical Devices

Regulatory decisions in relation to medical devices are made with reference to information from registries. Specifically, two UK implant registries currently collect detailed information about devices implanted – i.e. National Joint Registry (NJR) and the Breast and Cosmetic Implant Registry (BCIR) – see:

NJR: https://digital.nhs.uk/binaries/content/assets/legacy/pdf/1567662017spec.pdf

BCIR: BIR data collection form V1.3

In the case of NJR which has a mature dataset (data collected since 2003) this has allowed manufacturers and regulators to critically evaluate the post-market safety and performance of orthopaedic implants to make decisions about their continued use and regulatory status. See for example the following MHRA Medical Device Alerts relating to hip implants:

[22] Dixon et al; Rheumatology (Oxford). 2011 Jan; 50(1): 124–131

MDA/2013/010 – Adept hip system

MDA/2015/024 – Birmingham hip resurfacing system

In the case of BCIR – which only has around two years of data – it is not currently possible to gain detailed information about the long-term safety and performance of breast implants – but such analysis should be possible when the dataset has matured.

It is not possible to gain detailed information about the long-term safety and performance of devices covered by many of the other UK implant registries as they do not currently collect sufficiently detailed information about devices implanted.

The National Joint Registry (NJR) and the Breast and Cosmetic Implant Registry (BCIR) broadly meet most of the principles and criteria defined by International Medical Device Regulators Forum (IMDRF) in their three guidance documents on medical device registries – see:

(i) Principles of International System of Registries Linked to Other Data Sources and Tools - 30 September 2016

(ii) Methodological Principles in the Use of International Medical Device Registry Data – 16 March 2017

(iii) Tools for Assessing the Usability of Registries in Support of Regulatory Decision-Making – 27 March 2018

BCIR has not yet defined specific methods of “outlier detection” (as described in the methodological principles guidance) but the registry is currently considering how best to do this for breast implants.

Other UK implant registries do not in general meet a significant subset of the IMDRF principles/criteria, though this varies from registry to registry. Missing elements may include aspects relating to governance, transparency/reporting, collection of implant details and systematic/timely outlier analysis

Other registries (EU and international) exist that fully or partially meet the IMDRF requirements are set out in pages 8-15 in the Principles of International System of Registries Linked to Other Data Sources and Tools document above.

We are increasingly using information collected in registries as part of our proactive approach to vigilance. This is only possible where the data within it is of sufficient quality for us to draw meaningful conclusions.

12) What factors influence the decision on when to update Guidance, and how are adverse events reports weighted in this process given the known level of underreporting?

Medicines

The marketing authorisation holder has a legal obligation to inform the regulator of information which impacts on the risks and benefits of their medicinal product. They also have a responsibility to ensure that the Summary of Product Characteristics (SmPC) (formerly known as the Data Sheet in the UK) and the Patient Information Leaflet or PIL for each of their authorised products is kept up-to-date.

The role of the regulator is to ensure that the marketing authorisation for a medicine, as described in the SmPC and PIL, reflects the available data and outlines the terms under which the balance of benefits and risks of a medicine is positive. To assist marketing authorisation holders to develop both the SmPC and the PIL the European Medicines Agency has produced guidance documents on the information which is required.

The SmPC sets out the agreed position of the medicinal product as distilled during the course of the assessment process at the time of licensing. After licensing the SmPC is updated as new information on the risks and benefits of the product accumulate. The content of the SmPC cannot be changed except with the approval of the regulator.

The European Commission's Guideline on Summary of Product Characteristics states that the SPC should include *'all adverse reactions from clinical trials, post-authorisation safety studies, and spontaneous reporting for which, after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or on findings from epidemiological studies and/or on an evaluation of causality from individual case reports. Adverse events, without at least a suspected causal relationship, should not be listed in the SmPC.'*

The factors considered in deciding whether there is a causal association between a medicine and an adverse reaction include analysis of the strengths and weaknesses of the different types of evidence (including underreporting in the case of spontaneous reporting of adverse events). On occasion one strong case may be considered sufficient evidence for a causal association, in others multiple analyses of different data sets are required before a judgement can be made. Several factors are taken into account when assessing the likelihood of a causal association from spontaneous reporting data including the temporal association between the medicine (including evidence of dechallenge or rechallenge) and evidence of a dose relationship.

For medicines used in populations where the event in question occurs at an increased background rate, eg cardiovascular disease in patients treated with antidiabetics, data other than spontaneous reports would generally be required to reach a judgement as to whether the association seen between the medicine and the event was causal or not.

The concept of an evidence hierarchy with meta-analyses and systematic reviews at the top and case reports at the bottom has given way to integration of all available evidence, taking into account the strengths and weaknesses of each in the assessment of safety concerns.[23]

For significant changes to the SmPC, which are likely to have an impact on clinical practice, we seek the advice of the Commission on Human Medicines and its Pharmacovigilance Expert Advisory Group before reaching a conclusion. For example, the Pharmacovigilance Expert Advisory Group advised on the risk of drug induced liver injury with daclizumab, a

[23] Rawlins, M. De testimonio: on the evidence for decisions about the use of therapeutic interventions. Lancet. 2008 Dec 20;372(9656):2152-61.

treatment for relapsing multiple sclerosis. Their advice informed the UK position during EU discussions on this product.

The Patient Information Leaflet which accompanies the medicine is a full and comprehensible version of the SmPC which is written and designed in such a way to be clear and understandable, enabling users to act appropriately, when necessary with the help of health professionals. Amongst other things, the PIL contains information on all recognised adverse effects of medicines. PILs have been a legal requirement for all medicines since 1999.

PILs accompanying licensed medicines in the UK must comply with the requirements of both European and national (UK) law (Part 13 of the Human Medicines Regulations 2012). The information in the leaflet should be set out in a specific order as set out in Schedule 27 of those Regulations and the content must reflect the product licence details set out in the SmPC, presented using language that patients will be able to understand. All known side effects detailed in the SmPC must be also listed in the leaflet. There is a challenge in meeting the needs of all patients in one statutory leaflet, but recognising the often critical feedback from patients, we have worked with patient representatives to improve the comprehensibility of PILs, issuing guidance and a report, Always Read the Leaflet. This was developed with patients to coincide with a new legal requirement in 2010 to require the marketing authorisation holder to undertake testing of the PIL with patients to ensure accessibility and comprehensibility of the information provided.

The MHRA has also provided a comprehensive response to the European Commission consultation that led to their Report on the Shortcomings in the SmPC and the PIL and how they could be improved in order to better meet the needs of patients and healthcare professionals. An example of the changing UK approach to PILs is the use of headline statements in the PILs for SSRIs, following the review of adverse reactions in young people. Work is now beginning to explore how PILs can be made available electronically as part of the EU response to the 'shortcomings report' working with regulators across the EU.

Medical Devices

There are two main types of guidance for the safe use of medical devices that the MHRA has influence on:

- Firstly, MHRA, along with other EU competent authorities has regulatory responsibilities for reviewing the adequacy of the manufacturer's instructions for use as part of its review of the incidents it becomes aware of from the manufacturer's vigilance systems and its voluntary user reporting scheme – the Yellow Card scheme; and
- Secondly the MHRA's own voluntary guidance to users of medical devices, this is usually created to highlight common safety concerns across a class of devices and how to avoid them.

Manufacturer's Instructions for use and device labelling

The manufacturer's instructions for use (IFU) and labelling is the manufacturer's last line of safety control in the safe use of their device. The first being inherently safe design, and the second being protection measures, including alarms. The instructions for use will therefore frequently contain important information and instruction on the safe use of the device, which need to be adhered to in order to use the device safely. We do not regulate users but we have issued 'Off-label use of a medical device' guidance which says they should follow the manufacturer's instructions for use. If they use them in any other way, it's considered 'off-label use' and we tell them of the risks associated with this.

Post market safety information gathered by manufacturers as part of their post-market surveillance responsibilities provides valuable information concerning the accuracy, comprehensibility, and usability of the instructions for use and labelling of the device.

Manufacturers are obliged to report incidents where the instructions for use or the device labelling are contributing to or causing a reportable adverse incident to the relevant competent authority. Similarly, if adverse event reports from device users are sent to the competent authority there is a legal obligation for the competent authority to inform the manufacturer (anonymised as appropriate).

This feedback to the manufacturer and competent authority leads to ongoing review of whether the IFU guidance is fully fit for its purpose. Indeed, MHRA medical device specialists upon reviewing incidents and instructions for use will drive change in the instructions for use where they believe this is needed.

In weighing up the weight of evidence behind the adverse event it is possible (but unusual) for one single adverse event to provide sufficient evidence for the need to change the instructions for use due to the risks involved if a particular aspect of the IFUs is inadequate, for example if there are clear omissions of an important aspect in the safe use or even errors. On other occasions it might require several incidents to be reported before the need for greater clarity, or even the need for new guidance for a specific type of user becomes clear. Medical device specialists regularly conduct trending of adverse incidents and consider labelling in their trending activities.

As outlined in response to Q2, MHRA monitors relevant evidence from a range of sources as it becomes available, such as scientific papers, correspondence from the public, trends from adverse incidents and/or technical and safety data and does not rely solely on adverse incident data for raising a signal for further investigation. These different data sources add qualitatively different evidence data, for example, complication rates from hospital episode statistics, inform at device class level, unlike the majority of adverse incident data where the details of the device model are known. Gathering further sources of information helps us better understand the problem.

Furthermore, the continuous analysis of the collated adverse incidents allows MHRA to initiate new investigations where those data have identified emerging safety signals problems and/or unexpected reporting trends and then escalate if necessary to seek a resolution as quickly as possible. This may involve liaising with the manufacture(s) of the device and clinical experts.

Regulatory decisions are made on the totality of the evidence, considering the device, element, clinical practice and treatment pathways and taking appropriate action (see response to Q7).

As a consequence of our and other competent authorities' reviews, and the manufacturer own reviews, updates to instructions for use are a common inclusion in manufacturer's field safety corrective actions. MHRA also review every field safety corrective action, including those involving updates to the instructions for use, for adequacy in mitigating the identified risks, and will challenge the manufacturer if they believe the actions will be inadequate/insufficient. They also follow up the manufacturer's success in informing all users of the device via their field safety notices and will issue a medical device alert, if necessary, to reinforce the manufacturer's actions.

MHRA do want to improve the regulatory systems capabilities for identifying adverse trends in the use of devices, including concerning issues with the devices IFUs and labelling. This is why MHRA have been leading EU initiatives to:

- develop international terminology for medical device adverse events;

- overhaul the current manufacturer reporting form to include: adverse event terminology, similar incident data statistics along with denominator data, and Unique device identifiers. (See response to Q2); and
- explore techniques for safety signal detection as part of our patient safety and vigilance strategy.

MHRA have operational transformation plans to acquire automated statistical software to detect trends in a similar way to what is already possible for medicines due to the existence of international data standards for medicines ADR reporting. We also have plans to develop a new common case management system and risk assessment process with our medicines colleagues. Due to vast variety of ways in which medical devices are used, and the human factors involved in their use, including in their different healthcare settings, we plan to acquire text analytics capability to help us mine the richness of the free text in our incident reports. This will require significant investment financially and in staff resource, and so the pace will be determined by these aspects.

MHRA's own safety guidance/communications

MHRA publish a range of medical device safety guidance of their own (also see answers to Q7, Q8 and Q10). In general, they are but not isolated to:

Medical Device Alerts

- Medical Device Alerts (MDAs) are our most urgent important safety messages. They are issued when MHRA become aware of a serious medical device safety issue that requires action by healthcare professionals or other medical device users. They are most frequently issue to supplement a manufacturer's field safety notice. MDAs are distributed to the NHS in England via the Central Alerting System (CAS). MDAs remain valid unless they are updated or withdrawn. They are reviewed once they are five years old (and subsequently every year) and the lists on this website are amended accordingly.

Device Bulletins

- contain guidance and information on medical devices of a more general management interest. They are written as a result of experience gained from adverse incident investigations, our contacts with manufacturers and users, and other sources of information. Managing Medical Devices; guidance for healthcare and social services organisations gives further advice on off-label use.

One-liners

- This is a news sheet aimed at healthcare professionals, which highlights problems with the use of medical devices. All medical devices can fail for a number of reasons but an increasing number of incidents that result in significant morbidity or mortality arise out of user/device interface problems or because of poor practices. The aim of these news sheets is to detail briefly some of these problems in an attempt to make users more aware of what can go wrong. Some editions focus on a specific device or theme or are of interest to primary care trusts

Other safety information

- These are guidance documents that are not part of a series. They are written as a result of experience gained from adverse incident investigations, or contacts with manufacturers and users, our device evaluations and other sources of information.

Guidance documents are reviewed periodically based on the nature of adverse incident occurring, which due to the introduction of new device types and new use errors, may need to be revised to highlight new risks and how they can be avoided.

13) Does the fact something is a known teratogen affect pre- and post-marketing testing and guidance? In addition to inclusion of the information on the label, are other measures taken? Do you consider these measures to be sufficient? What factors are considered in the risk-benefit analysis and how are their weighted?

Medicines

Prior to authorisation of a medicine, pregnant women are rarely included in clinical trials which means there is generally limited human safety data and the risk of harm in pregnancy is often informed by non-clinical data. The need for non-clinical studies is laid out in ICH guidance (ICH M3 - Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals). Prior to the inclusion of pregnant women or women of child-bearing potential not using highly effective birth control in any clinical trial, all the standard reproduction toxicity studies (ICH S5) and the standard battery of genotoxicity tests (ICH S2) should be conducted. For a known or suspected teratogen, it is imperative to minimize the risk to the embryo or fetus and adequate precautions to exclude women of child bearing potential or prevent pregnancy must be made. The EU Clinical Trials Regulation (which came into force in 2016) makes specific provision for the inclusion of pregnant or breastfeeding women in clinical trials, subject to informed consent.

Post-licensing, known teratogens are usually contraindicated during pregnancy unless there are no other safe and effective treatments available and treatment is essential to maintain the health of the mother. When a product is so harmful (to the offspring) in pregnancy that use during pregnancy is considered never to be justifiable, a Pregnancy Prevention Programme (PPP) is usually considered a necessary part of the risk management plan (RMP) to ensure that pregnancy does not occur during treatment. Good Vigilance Practice Module XVI describes the requirements of a PPP, which combines the use of educational tools with interventions to control appropriate access to the medicine. A number of elements may be included in the PPP as required, such as: educational materials for healthcare professionals and patients to explain the risk of adverse pregnancy outcomes associated with exposure in utero; the requirement to use effective contraception; the requirement for a negative pregnancy test before treatment as well as assurance of absence of pregnancy upon repeat prescription; limiting prescriptions to a maximum of 30 days' supply (linked to pregnancy testing); controlled access at prescribing or dispensing level to ensure that a negative pregnancy test has been verified before prescription or dispensing of the medicinal product; and counselling in the event of inadvertent pregnancy and evaluation of the outcome of any accidental pregnancy.

It is a legal requirement for national competent authorities and marketing authorisation holders (MAHs) to actively monitor the outcome of risk minimisation measures such as PPP, described in the RMP. This may be achieved by performing post-authorisation safety studies (PASS) including drug utilisation studies (to monitor how medicines are used and whether exposures in pregnancy have occurred), or by disease or product specific pregnancy registries (to monitor pregnancy outcomes following exposure during pregnancy). All PASS protocols include milestones and MAHs provide updates to regulators on PASS results through regularly submitted periodic safety update reports. The final results of PASS of studies imposed on MAHs and considered essential to the balance of risks and benefits are considered by the European Pharmacovigilance Risk Assessment Committee (PRAC), which evaluates whether the results of the study have an impact on the marketing authorisation.

It is recognised that for a number of teratogenic products, the benefit risk balance is considered favourable in the context of an effective pregnancy prevention programme. Historically, thalidomide was associated with severe birth defects but both thalidomide and

its analogue lenalidomide have been proven highly effective agents for the treatment of multiple myeloma (MM, a cancer of the bone marrow). Therefore, both thalidomide and lenalidomide have been authorised for the treatment of MM but must be prescribed and dispensed according a detailed PPP, which applies to both men and women. Similarly, mycophenolate is effective in preventing transplant rejection but there is a significant risk of harm to a developing baby and of miscarriage if it is used in pregnancy. Therefore, mycophenolate must not be used during pregnancy unless there is no suitable alternative to prevent rejection of the transplant. Women able to have children should be tested before starting treatment to ensure that they are not pregnant, and both men and women must use highly effective contraception before, during and for a suitable period after treatment.

Emerging data relating to the effectiveness of existing risk minimisation measures is kept under close review as is new data on the risks associated with use during pregnancy for teratogens Evaluation of new data that becomes available may lead to further regulatory action being taken. For example, a Europe-wide review by PRAC of retinoid medicines (used mainly to treat conditions affecting the skin such as severe acne) was initiated by the UK due to concerns about the effectiveness of existing risk minimisation measures. This review, for which UK was one of the lead member states undertaking the assessment on behalf of the EU, concluded in March 2018 and confirmed that retinoid medicines taken orally are harmful to the unborn baby if taken during pregnancy. For this reason, the PRAC recommended that updates to the PPP for oral retinoids acitretin, alitretinoin and isotretinoin were needed to help ensure that these medicines are only used by women of child bearing potential, who are using effective contraception and also that they are not taken during pregnancy given the high risk of birth defects associated with these medicines. In May 2018, the safety of use during pregnancy of the antiretroviral medicine, dolutegravir, which is used to treat HIV infection was the subject of prompt review and regulatory action. This review was led by the UK followed results from an ongoing study in Botswana that suggested an increased risk of neural tube defects if dolutegravir is taken at the time of conception. None of the studies conducted prior to authorisation had raised any concerns about safety of use during pregnancy and this was the first post-marketing data source to raise a signal associated with use during pregnancy. Due to this new safety signal healthcare professionals were advised of this signal, through a Direct Healthcare Professional Communication, and that pregnancy should be excluded prior to starting treatment and that use of dolutegravir should be avoided prior to conception and during the first trimester (https://www.ema.europa.eu/news/new-study-suggests-risk-birth-defects-babies-born-women-hiv-medicine-dolutegravir).

In order to provide detailed guidance to industry on how best to monitor, further characterise and minimise the risk of harm of use of medicines in pregnancy, a Good Vigilance Chapter on pregnancy and lactation is in development. The European Medicines Agency is planning a public consultation on the Chapter to take place by the end of 2018, to ensure that the views of stakeholders are taken into account and the most helpful guidance is included in the published Chapter. This provides an important opportunity to review the approach to developing, implementing and monitoring the effectiveness of Pregnancy Prevention Programmes and achieve greater consistency based on the level of evidence.

Medical Devices

See Q20 for full details of pre and post-market requirements that also applies if there is a known teratogen in any medical device. However, we have provided some points below:

Pre-market:

If a manufacturer intends to supply medical devices in the UK or Europe they are legally required to comply with the Medical Devices Regulations 2002 (SI 2002 No 618, as amended) (MDR 2002). The MDR 2002 is legislation that transposes the EU Medical Devices Directive (93/42/EEC) into UK law.

The Medical Devices Directive does not exclude pregnant women from participating in clinical investigations during the pre-market phase of a medical device but the clinical investigation must be appropriate and a clear rationale provided.

Under the Directive, and in UK law, a manufacturer must inform the Agency if a clinical investigation in the UK is planned, and they must provide all relevant documents for an assessment of the safety and performance of the device. The assessment will determine if we have an objection or not and whether the proposed clinical investigation can be carried out in patients in the UK. See our guidance for more details.

The process also includes obtaining patient consent prior to the investigation being carried. Furthermore, Health Research Authority (HRA) approval also has to be obtained, which brings together assessment of governance and legal compliance, undertaken by dedicated HRA staff, with the independent ethical opinion by a Research Ethics Committee (REC).

Post market:

The Medical Device Directive lays down rules about chosen materials. In accordance with the essential requirements on the design and manufacture of medical devices: *"The devices must be designed and manufactured in such a way as to reduce to a minimum the risks posed by substances leaking from the device. Special attention shall be given to substances which are carcinogenic, mutagenic or toxic to reproduction. If the intended use of such devices includes treatment of pregnant or nursing women, the manufacturer must provide a specific justification for the use of these substances with regard to compliance with the essential requirements, within the technical documentation and, within the instructions for use, information on residual risks for these patient groups and, if applicable, on appropriate precautionary measures."*

Similarly, the new Medical Device Regulations also has rules about including detailed information, including test design, complete test or study protocols, methods of data analysis, and data summaries and test conclusions, regarding studies in relation to toxicity, including single-dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity and reproductive and developmental toxicity, as applicable depending on the level and nature of exposure to the device.

However, if a medical device is placed on the market for use and is known to contain teratogenic materials, it must be clear in the instructions for use on any potential side effects and if use in pregnant women is contraindicated for example. Any undesirable side-effects must constitute an acceptable risk when weighed against the benefits intended. The manufacturer must conduct a risk assessment to demonstrate that all hazards have been identified and that the risks have been removed or reduced as far as possible and constitute acceptable risks when weighted against the benefits to a patient. This forms part of a wider systematic risk management process of risk evaluation, control and reduction throughout the entire life-cycle of a device (pre and post production), and is carried out by the manufacturer, requiring regular systematic updating. This process is defined in 'ISO 14971 risk management of medical devices' and compliance with this standard is a key component in demonstrating compliance with the law.

14) Who determines what goes onto patient leaflets and data set? What are the roles of the manufacturer and regulator in this? Has this changed over time?

Medicines

The marketing authorisation holder has a legal obligation to inform the regulator of information which impacts on the risks and benefits of their medicinal product. They also have a responsibility to ensure that the Summary of Product Characteristics (SmPC) (formerly known as the Data Sheet in the UK) and the Patient Information Leaflet or PIL for each of their authorised products is kept up-to-date.

The role of the regulator is to ensure that the marketing authorisation for a medicine, as described in the SmPC and PIL, reflects the available data and outlines the terms under which the balance of benefits and risks of a medicine is positive. To assist marketing authorisation holders to develop both the SmPC and the PIL the European Medicines Agency has produced guidance documents on the information which is required.

The SmPC sets out the agreed position of the medicinal product as distilled during the course of the assessment process at the time of licensing. After licensing the SmPC is updated as new information on the risks and benefits of the product accumulate. Changes to the SmPC and the PIL can be made at the request of the marketing authorisation holder (MAH), voluntarily by the MAH at the request of the regulator or can be imposed by the regulator. The content of the SmPC cannot be changed except with the approval of the regulator.

The Patient Information Leaflet which accompanies the medicine is a full and comprehensible version of the SmPC which is written and designed in such a way to be clear and understandable, enabling users to act appropriately, when necessary with the help of health professionals. Amongst other things, the PIL contains information on all recognised adverse effects of medicines. PILs have been a legal requirement for all medicines since 1999.

PILs accompanying licensed medicines in the UK must comply with the requirements of both European and national (UK) law (Part 13 of the Human Medicines Regulations 2012). The information in the leaflet should be set out in a specific order as set out in Schedule 27 of those Regulations and the content must reflect the product licence details set out in the SmPC, presented using language that patients will be able to understand. All known side effects detailed in the SmPC must be also listed in the leaflet. There is a challenge in meeting the needs of all patients in one statutory leaflet.

In terms of changing approaches over time, recognising the often critical feedback from patients about PILS, we have worked with patient representatives to improve the comprehensibility of PILs, issuing guidance and a report, Always Read the Leaflet. This was developed with patients to coincide with a new legal requirement in 2010 to require the marketing authorisation holder to undertake testing of the PIL with patients to ensure accessibility and comprehensibility of the information provided. The impact has been some progress in the way PILs are written, but more needs to be done. In 2017, a report of the Academy of Medical Sciences on how we can all best use evidence to judge the potential benefits and harms of medicines made a number of recommendations and we are responding to those relating to patient information.

The MHRA has also provided a comprehensive response to the European Commission consultation that led to their Report on the Shortcomings in the SmPC and the PIL and how they could be improved in order to better meet the needs of patients and healthcare professionals. An example of the changing UK approach to PILs is the use of headline statements in the PILs for SSRIs, following the review of adverse reactions in young people.

Work is now beginning to explore how PILs can be made available electronically as part of the EU response to the 'shortcomings report' working with regulators across the EU.

Medical Devices

The current Medical Devices Directive 93/42/EEC (MDD) and new EU Medical Devices Regulation 2017/745 (MDR) both set out clear requirements in Annex I (available online, see paragraph 13) for the manufacturer to provide certain information to the patient or user with the device. This information, set out on the label and within the data in the instructions for use (IFU), needs to include (amongst other requirements):

- details on the safe and proper use of the device, taking account of the training and knowledge of the potential users;
- any warnings and precautions to be taken and;
- the identity of the manufacturer.

For certain types of medical devices including implantable devices, these instructions can be supplied in electronic form (Commission Regulation 207/2012). The provision of instructions for use in an electronic form can be beneficial for certain professional users and the purpose of the Regulation is to reduce the environmental burden and improve competitiveness by reducing costs whilst at the same time maintaining safety. There is even a suggestion that electronic instructions for use could improve levels of safety, given that electronic storage of information is less susceptible to loss, providing that sufficient safeguards are used. See our guidance on regulations for electronic instructions for use.

Regulators, such as the MHRA, designate notified bodies who are independent certification bodies. These notified bodies perform third-party conformity assessment activities including calibration, testing, certification and inspection. This includes assessing technical documentation relating to labels and instructions for use. Also see response to Q20.

Under the MDR, which will fully apply from May 2020, manufacturers will have to provide more information regarding the safety and clinical performance of a device, particularly for implantable and higher risk products. Furthermore, manufacturers of implantable devices will have to provide an implant card containing certain information on the identification of the device, the manufacturer, warnings and precaution measures and expected lifetime of the device to ensure traceability and provide rapid access to information for the patient. Also see response to Q31.

As described in response to Q12, if upon reviewing incidents and instructions for use, we will recommend change / improvements to the instructions for use as appropriate to ensure they meet the requirements stated above and as quickly as possible. If the manufacturer does not comply, we will consider enforcement action. See response to Q21.

15) When changes are made to prescription licensing, for example, restriction or removal for a specific indication, how do you communicate this? Who is responsible for compliance with the new regulations, and how is this monitored?

Medicines

The MHRA has several means by which we can routinely and directly communicate to the public and healthcare professionals on changes to a medicine's licence such as a restriction or removal of a specific indication, warnings or precautions, or addition of new safety information. The choice of method depends on several factors: the urgency of the safety issue, the nature of the action required, and the audience, amongst others. Where a new safety concern merits significant regulatory action, such as restricting or removing a specific indication, this is communicated proactively to relevant healthcare professionals. The MHRA uses the Central Alerting System for drug safety communications where the nature of the safety concern, the risk minimisation measures or the medicinal product(s) affected are such that they either result in significant restrictions to the use of a product or affect safe use of a very widely used medicinal product(s). Information is also made available via the MHRA website, our monthly drug safety bulletin, Drug Safety Update.

Information on licence changes is also disseminated by the marketing authorisation holder(s) in line with their legal obligations, in the form of a Direct Healthcare Professional letter. The MHRA agrees the content, timing and distribution list for this letter with the marketing authorisation holder(s). The final copy of the letter is also made available on the MHRA website and a link sent to healthcare professionals as part of the MHRA's regular electronic bulletin, Drug Safety Update.

For changes to medicine's licence where health care professionals' individual knowledge and practice are to be updated, the MHRA uses the Drug Safety Bulletin and liaises with relevant guideline owners including NICE as appropriate, and the British National Formulary. We participate in the regular meetings of the BNF committee to ensure the BNF is consistent with the up-to-date regulatory position.

Compliance of the healthcare system with safety alerts issued through the Central Alerting System is monitored during inspections by the Care Quality Commission (CQC), as part of their consideration of whether the service provided is safe. Risk minimisation for valproate as a recent and important alert has been included as a specific example in CGC inspections of GP practices and in August 2018 was cited as one of the factors in the assessment of a particular practice service as being inadequate.[24]

The bodies responsible for the regulation of registered pharmacists and doctors in the UK are the General Pharmaceutical Council (GPhC) and the General Medical Council (GMC) respectively. The MHRA regularly engages with these bodies on both general matters and particular issues.

The GMC also sets out standards for professional medical practice, including that reviewing a patient's medicines is particularly important where patients may be at risk or medicines have potentially serious side effects. Their guidance specifically makes reference to the MHRA Drug Safety Update. The GMC is also reviewing its consent guidance which will be open for consultation at the end of this month, including on the guidance for doctors on communicating with their patients, particularly in relation to explaining risk.

GPhC inspectors are looking for evidence of compliance with the valproate PPP during routine inspections of pharmacies and will be holding further discussions with the major pharmacy organisations and multiples to understand what further can be done to ensure

[24] Staunton Group Practice Inspection Report, CQC, published 13/08/2018 https://www.cqc.org.uk/sites/default/files/new_reports/AAAH4967.pdf

compliance. The GPhC has also issued its own communication to registered pharmacists highlighting the recent MHRA guidance and its own standards for pharmacy professionals on delivery of safe and effective care and that standards for registered pharmacies are being met.

As part of our pharmacovigilance system, MHRA monitors the effectiveness of risk minimisation measures and this includes through the evaluation of adverse drug reaction reports that are submitted via the Yellow Card Scheme, the published scientific and medical literature and also enquiries and correspondence from healthcare professionals and patients. Where the risk minimisation measures are thought likely to have a significant impact on public health, either due to the nature of the restrictions to the use of a product(s) or where the product(s) affected are widely used, then the MHRA may also conduct its own studies to evaluate the effectiveness of the risk minimisation measures through the use of real world data sources such as the Clinical Practice Research Datalink (CPRD). Such studies focus on clinical actions and safety outcomes and their results can be used to inform the need for further regulatory actions or communications.

This can be illustrated through the example of sodium valproate where evidence coming from the CPRD supported communications in Drug Safety Update[25] and also led to the issue of a Patient Safety Alert and informed the need for the initiation of the 2017 EU referral[26]. Another example is the class of retinoid medicines, for which a European review by PRAC was initiated due to concerns about the effectiveness of the pregnancy prevention plan programmes and which resulted in strengthened measures.

Medical Devices

Question not applicable as it relates to ‘prescription licensing’ which applies to medicines only.

[25] https://www.gov.uk/drug-safety-update/medicines-related-to-valproate-risk-of-abnormal-pregnancy-outcomes

[26] https://www.gov.uk/drug-safety-update/valproate-and-developmental-disorders-new-alert-asking-for-patient-review-and-further-consideration-of-risk-minimisation-measures

16) How does the Prescription Medicines Code of Practice Authority regulate free samples of prescription medicines? How is compliance monitored?

Medicines

The ABPI (Association of the British Pharmaceutical Industry) Code of Practice for the Pharmaceutical Industry sets out the requirements for supplying free samples of prescription medicines to healthcare professionals in clause 17. The Prescription Medicines Code of Practice Authority (PMCPA) investigates all complaints received about breaches of the Code. Details of their complaint procedures are available here.

The legal requirements for advertising medicines are set out in Part 14 of the Human Medicines Regulations 2012. The requirements for supply of free samples to healthcare professionals are set out in regulation 298. This provides that free samples may only be provided to persons qualified to prescribe medicines in limited quantities in response to a signed request. Further guidance is provided in section 6.12 of the MHRA Blue Guide.

The advertising of medicines in the UK is controlled by long-established systems of self-regulation underpinned by the statutory role of the MHRA. The ABPI Code of Practice reflects the legal requirements for advertising medicines as set out in Part 14 of the Human Medicines Regulations 2012. It also extends beyond this to provide standards and detailed advice to ensure that pharmaceutical companies both comply with the law and operate in a responsible, ethical and professional manner.

Medical Devices

Question not applicable as applies to medicines only.

17) If you receive referrals from PMCPA for non-compliance with the Memorandum of Understanding on Prescription Medicines, what actions are taken?

Medicines

Complaints made about non-compliance with the ABPI Code of Practice are investigated by the Prescription Medicines Code of Practice Authority (PMCPA) in accordance with their complaint procedures, available here. Individual case reports are published at the end of each case, with full details of the consideration of the evidence submitted. In addition the PMCPA issues an annual report on actions taken. The report on the 76 complaints received in 2016 is available here. The PMCPA has a range of sanctions available to deal with non-compliance including requirements to issue a corrective statement or undergo an audit. The PMCPA would only refer a company to MHRA in the event of persistent problems leading to suspension or expulsion from membership of the ABPI or if the company withdraws their agreement to participate in the PMCPA complaint procedure. This is set out in the section of the Memorandum of Understanding on the role of the PMCPA and the ABPI Code.

Any complaint referred to the MHRA because the company does not participate in the PMCPA complaint procedure would be investigated in accordance with normal MHRA procedures. These are set out in section 8.4 of the MHRA Blue Guide. If a company is referred because it has been suspended or expelled from ABPI membership, MHRA would consider whether additional steps are required to assure compliance with the legal requirements on medicines advertising. Steps may include prior vetting of the company's advertising, inspection of company procedures or other measures as required. Details may also be provided to the MHRA Inspectorate to inform their risk-based approach to inspection scheduling. A report on MHRA advertising regulatory activities in 2017 is available here.

Medical Devices

Question not applicable as applies to medicines only.

18) Please outline the process for recommending off-label use of drugs (for example the use of valproate medications for bipolar disorder). How frequently does this occur? Where does liability for adverse events lie, if a clinician is following NICE guidelines for off-label use?

Medicines

A marketing authorisation (product licence) defines a medicine's terms of use and its Summary of Product Characteristics outlines, among other things, the indication(s), recommended dose(s), contraindications, and special warnings and precautions for use on which the licence is based is in line with such use that the benefits of the medicine have been judged to outweigh the potential risks. Furthermore, a licensed medicine has been assessed for efficacy, safety, and quality; has been manufactured to appropriate quality standards; and when placed on the market is accompanied by appropriate product information and labelling.

However, there are clinical situations when the use of unlicensed medicines or use of medicines outside the terms of the licence (ie, 'off-label') may be judged by the prescriber to be in the best interest of the patient on the basis of available evidence and absence of a suitable licensed product. We do not have data on how frequently off-label use of medicines occurs but such practice may be more common in certain areas of medicine, for instance, in paediatrics where lack of availability of age-appropriate formulations means that many medicines used in children are used off-label or are unlicensed. There aren't good data on exactly how frequently an unlicensed medicine is prescribed.

When prescribing an unlicensed medicine or a medicine off-label the healthcare professional is effectively taking responsibility for the safety of the medicine, as set out in this article in Drug Safety Update and in guidance from the General Medical Council. Prescribers should pay particular attention to the risks associated with using unlicensed medicines or using a licensed medicine off-label. These risks may include: adverse reactions; product quality; or discrepant product information or labelling (eg, absence of information for some unlicensed medicines, information in a foreign language for unlicensed imports, and potential confusion for patients or carers when the Patient Information Leaflet is inconsistent with a medicine's off-label use). The General Medical Council (GMC) guidelines on prescribing include a description of the prescriber's responsibilities when prescribing a medicine off-label as follows: '*An unlicensed medicine may be prescribed where, on the basis of an assessment of the individual patient, the prescriber concludes, for medical reasons, that it is necessary to do so to meet the specific needs of the patient'*.

Valproate (under the brand leader trade name Depakote and a number of generic products, Convulex, Orlept, Noridem, Episenta and Epival) is licensed for the following indication 'Treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated. The continuation of treatment after manic episode could be considered in patients who have responded to Depakote for acute mania.', therefore the use of valproate in bipolar disorder would not be considered off-label.

Medical Devices

Question is directed to medicines only but 'off-label use' of medical devices is covered in Q12.

19) Can you give us an overview of your role in the modified prescription event monitoring system and do special provisions apply to the system if a medicine is a suspected or known teratogen?

Medicines

Modified Prescription Event Monitoring studies are undertaken (among other types of study) by the Drug Safety Research Unit (DSRU) in Southampton, an independent academic unit linked as an associate department of the School of Pharmacy and Biomedical Sciences to the University of Portsmouth.. The MHRA can require a Marketing Authorisation Holder to conduct post-authorised safety studies (PASS) to answer a particular question about the safety of a medicinal product (see question 20). One reason for requiring a PASS could be to expand information on safety in pregnancy. Modified Prescription Event Monitoring (M-PEM) studies are designed to answer specific research questions and therefore if a study was proposed to address questions about safety in pregnancy it would have to be designed appropriately to ensure capture of the data. If the MAH proposes an M-PEM study as a way of answering the scientific question, we will assess both the protocol, to decide if the choice of approach is appropriate to address the study questions, and any results of the study.

Medical Devices

Question not applicable as applies to medicines only.

20) Please define circumstances in which you would request manufacturers to carry out pre- and post- marketing surveillance.

Medicines

Manufacturers are legally required through the marketing authorisation application process to provide the relevant regulatory authority with all information for evaluation of the benefit risk of a medicine. This includes animal study and clinical trial results which are both favourable and unfavourable. Manufacturers are also legally required to submit a risk management plan (RMP) which includes information on the known safety profile of a medicine; how any risks will be prevented or minimised; plans for studies to gain more knowledge about the safety and efficacy of the medicine and how the effectiveness of any risk minimisation measures will be measured. This is submitted and assessed at the time of licensing.

Manufacturers are always required to carry out post-marketing surveillance on the products for which they hold a marketing authorisation. EU law requires each marketing authorisation holder (manufacturer), national competent authority and EMA to operate a pharmacovigilance system (to conduct post-marketing surveillance). The overall EU pharmacovigilance system operates through cooperation between the EU Member States, EMA and the European Commission. The responsibilities of all parties are outlined in Good Vigilance Practices.

The legislation includes provision for post-authorisation safety studies (PASS). These may be required of the marketing authorisation holder by the regulator as part of a risk management plan or conducted voluntarily by the marketing authorisation holder. PASS may be required to fulfil the following objectives:

- to quantify potential or identified risks which have been raised by the RMP;
- to evaluate the risks of a medicinal product used in a patient population for which safety information is limited or missing (e.g. pregnant women, specific age groups, patients with renal or hepatic impairment or other relevant comorbidity or co-medication);
- to evaluate the risks of a medicinal product after long-term use;
- to provide evidence about the absence of risks;
- to assess patterns of drug utilisation (e.g. collection of information on indication, off-label use, dosage, co-medication or medication errors in clinical practice that may influence safety, as well as studies that provide an estimate of the public health impact of any safety concern); and
- to measure the effectiveness of a risk management measures.

Scientific guidance on the design and conduct of studies is available to marketing authorisation holders from the Scientific Advice Working Party and Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA. Protocols for imposed PASS are subject to consideration and approval from PRAC.

Medical Devices

Pre-market:

If a manufacturer intends to supply medical devices in the UK or Europe they are legally required to comply with the Medical Devices Regulations 2002 (SI 2002 No 618, as amended) (MDR 2002). The MDR 2002 is legislation which transposes the EU Medical Devices Directive (93/42/EEC) into UK law.

To do so a manufacturer must meet a large number of requirements prior to placing a device on the market. Principally, this constitutes meeting the relevant essential requirements of Annex I in the MDD which cover the necessary safety and performance-related device features. Furthermore, manufacturers must hold clinical data to support claims made for all types of medical devices. This clinical data is set out in a clinical evaluation, which is an assessment and analysis of clinical data to verify the clinical safety and performance of the device. Typically, a clinical evaluation will include a clinical investigation specific to the device where a medical device has new design features or uses new materials (it is important to know that under the Directive and UK law the manufacturer must inform MHRA if a clinical investigation in the UK is planned, and they must provide all relevant documents for a robust assessment by MHRA of the safety and performance of the device. The assessment will determine if MHRA has an objection or no objection and whether the proposed clinical investigation can be carried out in patients in the UK. See our guidance.). For higher risk devices, including mesh, manufacturers must have the product's safety and performance assessed by an independent certification body, called a notified body, before the product can be placed on the market.

A notified body's tasks will vary depending on the classification of the products concerned, but typical activities include an examination of the design dossier relating to each type of product, an assessment of the full technical information, and manufacturer inspections.

The process also includes obtaining patient consent prior to the investigation being carried. Furthermore, Health Research Authority (HRA) approval also has to be obtained, which brings together assessment of governance and legal compliance, undertaken by dedicated HRA staff, with the independent ethical opinion by a Research Ethics Committee (REC).

A clinical investigation can be conducted anywhere in Europe and will be assessed by the Competent Authority in the countries it is to be carried out in. So, this means not all European clinical investigations will occur in the UK. Manufacturers may also carry out clinical investigations anywhere else in the world.

Post-market:

Once a medical device has been placed in the UK market with a valid CE mark, the manufacturer must continually monitor the performance of their device. They must submit vigilance reports to us when certain incidents occur in UK involving their device and take appropriate safety action when required. This ensures the device meets appropriate standards of safety and performance for as long as it is in use. The current European Commission's detailed Vigilance guidance covers the definition of an adverse incident and how and when a manufacturer should report one to MHRA. Manufacturers are also encouraged to send us reports if in doubt as to whether they fit the relevant reporting criteria.

Additionally, we monitor adverse incidents reported though our voluntary Yellow Card Scheme but we strongly encourage reporting by anyone, patient, carer or healthcare professionals. All these reports (anonymised as appropriate) are sent to the relevant manufacturer to feed into the vigilance system.

The new EU Medical Devices Regulation 2017/745 (MDR) came into force on 25 May 2017, which is when the three-year transition period began. The MDR will fully apply in EU Member States from 26 May 2020. During the transition period, devices can be placed on

the market under the current EU Directive, or the new Regulations (if they fully comply with the latter, including meeting post-market surveillance and vigilance obligations).

Under the MDR, post-market surveillance and vigilance reporting requirements are more stringent. This includes new vigilance reporting timescales and clearer requirements for a manufacturer's post-market surveillance system. High risk devices will be subject to a higher level of scrutiny in both pre- and post-market surveillance, including the level of clinical evidence required. For class III devices which includes mesh, manufacturers will be required to summarise the main safety and performance aspects of the device and the outcome of the clinical evaluation in a document that should be publicly available. This document is known as the summary of safety and clinical performance (SSCP). The SSCP is part of the documentation to be submitted to the notified body (independent certification bodies designated by the national regulator) involved in the conformity assessment and shall be validated by that body. The manufacturer will also be required to state on the label or instructions for use where the summary is available.

A new requirement for manufacturers of higher risk devices (Class IIa and above) has been introduced. The manufacturer will need to prepare a periodic safety update report ('PSUR') for each device summarising the results and conclusions of the analyses of the post-market surveillance data gathered, together with a rationale and description of any preventive and corrective actions taken. Manufacturers of class IIb and class III (which will include mesh) devices are required to update the PSUR at least annually.

The new Regulation also strengthens post-market requirements in the form of a post-market clinical follow-up (PMCF). This is a continuous process that updates the pre-market clinical evaluation and requires manufacturers to proactively collect and evaluate clinical data from the use in or on humans of the CE marked device. PMCF is particularly relevant for medical implants for long-term assessment of the ongoing safety and performance of a device.

21) Please define the source and scope of your powers when asking manufacturers the reasons behind device withdrawals.

Medical Devices

If a manufacturer intends to supply medical devices in the UK or Europe they are legally required to comply with the Medical Devices Regulations 2002 (SI 2002 No 618, as amended) (MDR 2002). The MDR 2002 is legislation which transposes the EU Medical Devices Directive (93/42/EEC) into UK law.

The Medical Device Directive legally requires the manufacturer to report to MHRA "any technical or medical reason leading to a systematic recall of devices of the same type by the manufacturer. Those reasons are any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the instructions for use which might lead to or might have led to the death of a patient or user or to a serious deterioration in his state of health." We may take any further action if deemed appropriate, including gathering more information or publishing a safety message as described in previous responses above.

Device removals from the market for purely commercial non-safety related reasons are not included.

The MHRA performs market surveillance which involves checking and ensuring that devices comply with the MDR 2002 (example of this is shown in Q1 timeline for mesh). This ensures that devices placed on the market do not endanger public health or patient safety. The MHRA monitors relevant evidence from a range of sources as it becomes available, such as scientific papers, signals from adverse incidents and/or technical and safety data.

If the devices on the market do not comply with the law for any reason, we will work with the manufacturers and take reasonable steps to bring the device back into compliance as quickly as possible. We will:

1. issue a compliance and enforcement notice (COEN) to the relevant EU Competent Authority (if the manufacturer or authorised representative is not in UK) with our findings and ask them to resolve as quickly as possible with the manufacturer and Notified Body. Conversely, we receive COENs to act upon too.

2. perform direct, on-site audits of UK manufacturer or its UK authorised representative. We share our findings of the audit with the relevant Notified Body as well as any agreed action plans which then become the responsibility of the Notified Body to verify implementation. This UK process is being established further.

If the manufacturer fails to co-operate and continues to place a non-compliant product on the market, or there is a serious risk to public health, if there is sufficient evidence we will consider using our enforcement powers to ensure the protection of public health and patient safety. Our powers for inspection and enforcement are provided by the Consumer Protection Act 1987 and the Consumer Rights Act 2015. This might include prohibiting or restricting the device being made available on the UK market, withdrawing the device from the market or to recalling it until the manufacturer cooperates or provides complete and correct information.

These activities form part of our market surveillance obligations under EU regulation 765/2008 and we undertake them in accordance with the statutory principles of the Regulators' Code.

Any decision on regulatory action would take into account the protection of public health and criteria such as causality, detectability and probability of recurrence of the problem, frequency of use of the device, probability of occurrence of direct or indirect harm, the severity of that harm, the clinical benefit of the device, intended and potential users, and population affected

The new EU Medical Devices Regulations 2017/745 (MDR) entered into force on 25 May 2017, which is when the three-year transition period began. Therefore, the MDR will fully apply in EU Member States from 26 May 2020. During the transition period, devices can be placed on the market under the current EU Directive, or the new Regulations (if they fully comply with the latter).

The MDR introduces enhanced market surveillance responsibilities for competent authorities, shifting market surveillance work to a more proactive approach and reinforcing the rights and obligations of the national competent authorities (see Q1 for role of competent authorities), to ensure effective coordination of their market surveillance activities (also see response to Q9). The MDR introduces clearer obligations to conduct announced and unannounced inspections on manufacturing and clinical investigation sites. Furthermore, each competent authority will be required to produce an annual surveillance plan and allocate appropriate resources to perform this task and prepare an annual summary of the results of their surveillance activities. Closer coordination between national Competent Authorities through information exchange, joint working, coordination and communication of market surveillance activities aims to ensure a consistently high level of health and safety protection within the internal market, as well as to more efficient use of resources and expertise at national level.

22) There are known examples of manufacturers failing in their duty to report adverse events, such as PIP failing to report to the French regulators. Are there other examples of this, and if so, how frequently does this type of behaviour occur?

Management of critical pharmacovigilance issues identified through inspection

A company's ability to collect and report adverse events is reviewed as part of MHRA pharmacovigilance inspections; although this is an uncommon occurrence, critical inspection findings have been raised where significant failures to report adverse reactions or insufficient processes to collect such information, have been identified.In these situations, the primary focus is to ensure companies come into compliance as rapidly as possible, deciding on whether any immediate action is necessary to protect public health, and where appropriate considering whether any further action is required.

MHRA Inspectors work with the company to ensure that adequate corrective and preventative action (CAPA) plans are implemented to remediate the non-compliance; these plans are subject to approval by the MHRA and reviewed during subsequent inspections.

Critical inspection findings are also referred to the MHRA Inspection Action Group (IAG) – IAG is a non-statutory, multi-disciplinary group which advises the MHRA director of inspection, enforcement and standards on recommendations for regulatory or adverse licensing action. A wide-range of action are available to IAG.

One example where a failure to report adverse events was identified was during the 2012 MHRA inspection of Roche; this inspection reported critical findings associated with pharmacovigilance activities. At the time of the inspection, the company identified approximately 80,000 reports for medicines marketed by Roche in the United States that had been collected through a Roche-sponsored patient support programme, but which had not been evaluated to determine whether they should be reported as suspected adverse reactions to the European Union (EU) authorities. These included 15,161 reports of death of patients. It was not known whether the deaths were due to natural progression of the disease or had a causal link to the medicine.

Other deficiencies identified related to the evaluation and reporting to national medicines agencies of suspected adverse reactions from their reporting systems (around 23,000) and clinical trials (around 600).

The MHRA supported discussions at EMA Committees to agree specific remediation actions for Roche. The MHRA conducted an EMA CHMP (Committee for Medicinal Products for Human Use) requested re-inspection of Roche in 2013 which identified critical findings associated with the remediation of issues reported during the 2012 inspection. In December 2014 a CAPA plan was agreed with Roche to ensure adequate remediation of the issues identified.

Given the serious nature of the findings, in October 2012 the EMA initiated an infringement/penalties procedure against Roche (within the legal framework of Regulation (EC) No 658/20), at the request of the European Commission, to investigate Roche's failure to comply with pharmacovigilance requirements.

In 2017 the EU Commission closed the infringement procedure against Roche, after considering all the evidence available and being satisfied with the company's remedial actions. In a written statement submitted to the Commission, Roche said: "Roche accepted all the inspection findings. It took them extremely seriously and fully understands the EMA's and Commission's concerns. It has worked diligently to remediate the deficiencies as quickly as possible and also to enhance the company's medical compliance and PV systems to prevent any recurrence. While it has come a long way, the company knows that its efforts to

enhance its systems and to maintain the trust of all stakeholders must continue. It is committed to working with the authorities to ensure it becomes, and then remains, a leader in the field."

In another example, the 2013 MHRA inspection of Omega Pharma revealed that the company had made insufficient progress in remediating previously identified critical findings which now constituted serious and persistent non-compliance with EU and UK pharmacovigilance regulations. These non-compliances included inadequate systems for the collection of suspected adverse events.

Therefore, a UK infringement notice was served to the company, pursuant to regulation 206 of the Human Medicines Regulations 2012. The notice was published on the MHRA website and shared with the EMA and EU Commission.

The notice described the measures the company was required to implement and the further action that the MHRA may take if such measures were not implemented (action against licences and referral for criminal prosecution).

Omega Pharma submitted responses to the infringement notice and inspection findings; the implementation of the stipulated measures was reviewed during the MHRA re-inspection of Omega Pharma Limited in 2015 and the critical issues were considered to be resolved.

Medical Devices

The current Medical Device Directive and new EU Medical Devices Regulations place mandatory reporting of certain adverse incidents that occurred in the UK to MHRA as described in the current European Commission's detailed guidance on medical devices vigilance system. It defines what, how and when a manufacturer reports an adverse incident, and the significant role regulators have in this system to protect public health. The present guidelines are part of a set of guidelines relating to questions of application of the Directives. The guidelines are not legally binding but are used by all those involved (manufacturers, regulators, users concerned with safety, and notified bodies) to ensure the system is applied accordingly.

We do however find some manufacturers misunderstand what is expected of them, when to report and/or what is deemed reportable to MHRA under the above system. We have contacted them and provided advice, so they comply with the requirements. A small number of manufacturers have shown not to comply, and we have taken reasonable steps to bring them into compliance with the requirements for reporting to MHRA (see response to Q21).

The Poly Implant Prothèse (PIP) case was an issue relating to fraud. To the best of our knowledge, no similar event of fraud has occurred since the PIP case.

The Lord Howe review of the actions by us and the Department of Health in relation to PIP silicone breast implants, highlights that it was one of deliberate fraud by the manufacturer who purposefully misled European regulators. Regulation alone cannot prevent fraudulent activity such as this. The collaborative effort of sharing concerns between regulators led to the French regulator's unannounced inspection of the manufacturer in March 2010, where the use of non-approved filler material was discovered.

In 2017, we understand the German Federal Court of Justice found that TÜV Rheinland (German Notified Body for PIP) had no liability. Furthermore, we believe the French Supreme court has recently finalised its rulings which recognised PIP TÜV Rheinland were a victim of fraud.

In light of the Poly Implant Prothèse (PIP) implant fraud, the new EU Medical Devices Regulation (MDR) post-market surveillance and vigilance reporting requirements are more stringent. This includes new vigilance reporting timescales and clearer requirements for a manufacturer's post-market surveillance system (see response to Q21).

23) In your view, what are the priorities for future research related to the interventions and issues raised by the Review?

Risk communications

Across the healthcare sector, there appears to be an inconsistent approach to safety messages by national bodies. Messages may not always be targeted to the staff best placed to act, and there is difficulty in knowing if the intended audiences have been reached and the expected actions implemented. Messages are sent in different formats, using different terminology to describe their importance and urgency, and from different mailing databases. As a result, national safety messages relating to medicines and medical devices are not acted on as promptly and effectively as they could be, and this can impact adversely on patient safety.

To start to address these issues, the MHRA brought together a group of high-profile leaders in healthcare and researchers to discuss how systems can be improved to improve message delivery and support staff to work safely, how we could reach a consensus on the changes we would want to see and how we could measure if the messages are being received, understood, and acted upon, how safety messaging can be supported by better education of healthcare professionals, and what the role of newer digital solutions is. Details on the Future Safety Messaging event and the workshops held can be found here.

Following this event, the Department of Health and Social Care asked the NHS Improvement Patient Safety Team to establish a National Patient Safety Alert Committee (NaPSAC) to agree common criteria for safety-critical alerts requiring coordinated action by organisations. MHRA has director-level representation on this important committee. A key element that emerged from the Future Safety Messaging event is better message design, to ensure that safety-critical alerts requiring coordinated organisational action stand out from other communications, provide clear information on actions required, and are instantly recognisable.

In addition, as part of this work, MHRA is to establish a new healthcare sector partnership which is looking at the redevelopment of the Central Alerting System (CAS) and improvements to safety messages which are informative and educational and are designed to prevent further escalation into mission critical alerts i.e. those messages not in the remit of NaPSAC. This includes the devolved nations and the future development of the Central Alerting System which MHRA hosts and manages and is the channel used to send alerts to the health sector.

Through the work on valproate, a relationship has also been established with the Behavioural Insights Team (BIT, formally known as the Nudge Unit in Cabinet Office) who use insights from behavioural science research to improve outcomes by introducing a more realistic model of human behaviour to policy development and implementation, enabling people to make better choices for themselves. The MHRA intend to continue working with this organisation to further research effective communications to patients, the public, and healthcare professionals and to gain from the evolving science of implementation.

Special attention is also being paid to messages directed to pregnant women and those planning pregnancy as well as relevant healthcare providers. The MHRA has supported independent research to understand the barriers to reporting with the aim of developing a communications campaign that encourages reporting with a focus on women taking medicines in pregnancy. The final insight report was received in early October. We are intending to use the research to develop a campaign in early 2019 to encourage reporting by women and healthcare professionals. The MHRA is also participating in a European-wide social media ADR campaign in the week 19-23 November which focuses on women taking medicines in pregnancy, women giving medicines to children, and advice for healthcare professionals.

Monitoring impact and outcomes and measuring the effectiveness of risk minimisation and communications related to the use and safety of medicines

Critical to supporting risk communications and increasing the effectiveness of messaging, as highlighted though the ongoing research into how to deliver effective safety communications, is access to data on the impact of the measures being communicated on the understanding of risk, clinical decision-making, and patient safety. This is also vital in helping to ensure a proactive rather than reactive approach to patient safety whereby deficiencies in actions leading to a lower than expected impact or unintended consequences can be rapidly identified and fed back into decision-making to support further timely and more refined actions by regulators, industry, the healthcare system, and healthcare providers as required.

Such work has been undertaken by the MHRA for a number of years but the value of having rapid direct access to quality data in this regard has been highlighted again through the ongoing work related to valproate. Therefore, based on experiences to date the MHRA is developing a strategy for how we will further develop our capability and methodology in monitoring the effectiveness of risk minimisation. This will include consideration of when there is greatest need for the MHRA to monitor the effectiveness of risk minimisation and to what extent, how we can increase our access to data that can support this monitoring, where we can support additional relevant data collection, how we should optimally design such monitoring, how we should define success, how long monitoring should continue for, how we can work most effectively with the healthcare system.

Sodium Valproate

The MHRA continues to prioritise the conduct of research into the implementation of the Pregnancy Prevention Programme and the effectiveness of the risk minimisation measures and related communications in ensuring all women of child bearing age are aware of the risks associated with the use of valproate in pregnancy, in substantially reducing prescribing of valproate in females where alternatives are effective, and in eliminating exposures during pregnancy. The MHRA continues to utilise the Clinical Practice Research Datalink as well as working with other data holders, including the NHS and Devolved Administrations and healthcare professional organisations, in order to adequately capture information on the different aspects of risk minimisation and ensure feedback of the findings to all stakeholders to enable informed decision-making and support the required changes in clinical practice.

Following discussion and agreement with the EMA Pharmacovigilance Risk Assessment Committee (PRAC) further studies into potential transgenerational transmission and effects following parental exposure have been prioritised for rapid research. Both issues were discussed within the EU referral procedure that concluded this year and raised in the EMA public hearing, but it was agreed at that point that the body of cumulative evidence was insufficient to support a causal association. However, the evidence base for both issues remains small and therefore rapid generation of new evidence is required. The European regulatory network, including the UK, is working with a range of experts to proactively advise marketing authorisation holders on what studies are required, and how they should be designed, as confirming or refuting these potential risks is of high importance to the benefit risk profile of valproate and the implementation of effective risk minimisation if needed.

While it is known that the risks associated with the use of valproate in pregnancy are present regardless of dose, the use of valproate, as for all medicines, at the lowest effective dose is considered best clinical practice. Further data on the magnitude of risk according to dose could potentially be of value in further refining risk minimisation measures and informing clinical decision-making.

While a better understanding of how to switch safely and effectively between anti-epileptics will have less impact from a regulatory perspective on the licencing of valproate it is felt that this is an important area within clinical practice and will help support risk minimisation.

It is also considered, particularly from a patient perspective, that clinical agreement regarding a definition of Fetal Valproate Spectrum Disorder is important. From a regulatory perspective, if a definition can be agreed this will help contribute to detailed risk communication. The MHRA maintains close ties with key UK academics working on this definition, and other research into the safety of valproate and other anticonvulsants in pregnancy, to ensure that we are able to rapidly incorporate new evidence into regulatory guidance and communication as appropriate.

Hormone Pregnancy Tests

The Commission for Human Medicines established a new ad hoc expert group specifically to consider recently published non-clinical data from the University of Aberdeen on developmental defects in zebrafish embryos following exposure to a norethisterone acetate/ethinylestradiol mixture. The expert group concluded that these data have no implications for medicines currently on the market and made no recommendations for further work. As with any other medicine, if relevant new evidence emerges this will be carefully evaluated in line with usual MHRA practice.

Medicines in pregnancy

The MHRA is currently working on a number of initiatives to help strengthen the systems in place for detecting, evaluating, managing and communicating risk with exposure to medicines in pregnancy as recommended by the Commission on Human Medicines Expert Working Group on Hormone Pregnancy Tests. In terms of further scientific research, these include bringing together an expert group to advise on promoting and facilitating better and wider data collection directly from patients, healthcare professionals, and the healthcare system; improving linkage of such data; enabling timely access to data; and increasing the robustness of the evidence generation.

In addition, the MHRA is organising an international scientific workshop in January 2019 to consider how results from studies in pregnant animals can be made more accessible to help predict and assess potential effects from medicines in pregnancy and the feasibility of using computer modelling and molecular structure alerts to generate safety signals from animal and in vitro data as well as a strategy to coordinate and promote research on mechanisms of teratogenicity in early embryonic development and drug transporter expression in the placenta.

The MHRA is also working with other EU National medicines regulators and the EMA to devise specific requirements for industry and a number of supporting guidance documents including new Good Vigilance Practice guidance specifically for medicines use in pregnancy. The MHRA is also prioritising a number of initiatives to improve the quality and quantity of data related to the use of medicines in pregnancy via the Yellow Card scheme and to increase the timeliness and extent of expert scientific review of individual cases reports.

The MHRA has also committed to contribute to the Innovative Medicines Initiative (IMI) funded project "Continuum of Evidence from Pregnancy Exposures, Reproductive Toxicology, and Breastfeeding to Improve Outcomes Now" (ConcePTION).

Abdominal and vaginal pelvic mesh

Much of the risk communications section above applies. See response to Q30 for ongoing work to improve reporting and dissemination of safety messages.

We would like to comment on the desirability of progressing efforts to ensure that the details of mesh implants are included in electronic patient records in order to facilitate longitudinal research. The Scan-for-Safety programme (detailed in our response to Q31) and provisions in the new medical devices legislation relating to unique device identifiers (UDI) will act as enablers for accurate recording of implant details and allow a variety of research activities which can answer questions about the relative effectiveness of interventions, including those with or without devices, and long-term outcomes for patients. This would complement, and possibly in the longer-term substitute for, the use of specific registries which measure outcomes for interventions such as those involved in managing stress urinary incontinence (SUI) and pelvic organ prolapse (POP).

Our efforts to enhance the accuracy capturing of data collected in regulatory datasets have included vigorous and active support for the Scan4Safety programme, leadership of the International Medical Device Regulators' Forum (IMDRF) work on Terminologies for Adverse Incident Reporting and participation in the task force working on harmonising best practice for registry development (see response to Q11).

MHRA has held discussions on the potential to use larger datasets in support of our responsibilities for market surveillance and vigilance includes using artificial intelligence to gain insights into population health to add to the MHRA business plan objective to '*Work with UK government and healthcare organisations to expand use and future capability of UK healthcare datasets and systems data capture for medicines and medical devices in order to widen and strengthen the use of real- world evidence*'. This in response to Lord O'Shaughnessy's challenge to NHS England's Chief Clinical Information Officer, Simon Eccles *'to develop a piece of exploratory work to look at using existing data to identify trends in adverse events from medicines and devices'*

This would translate to developing better tools for life-cycle management of both medicines and devices as well as earlier signal detection in the case of product performance issues.

SODIUM VALPROATE & HORMONE PREGNANCY TESTS QUESTIONS

24) Do you have archived minutes from the following meetings, relevant to sodium valproate use in pregnancy, and hormonal pregnancy tests: a. Committee on Safety of Drugs/Committee on Safety of Medicines, Adverse Safety Reactions Subcommittee (1968 to 1978); and b. Joint Standing Committee on Proprietary products (the 'McGregor Committee') (1967 - 1971)

a) Committee on Safety of Drugs/Committee on Safety of Medicines, Adverse Safety Reactions Sub-committee (1968 to 1978)

Sodium valproate

In the time period specified, Sodium valproate was considered by the Committee on Safety of Medicines in January 1972, May 1972, June 1972, June 1973, July 1973, August 1973, March 1974, August 1974 and September 1974. These minutes are attached within a separate file (see 'Valproate attachment annexes for Q1 & Q24.pdf'). In addition, valproate was considered by the Adverse Safety Reactions Subcommittee in 1974. We are trying to retrieve these minutes from the National Archive.

Hormone Pregnancy Tests

Due to the length of time that has elapsed since HPTs were on the UK market, very little historical documentation on these products was retained by the Government. For the EWG review of HPTs a search of the national archives was therefore conducted by a professional researcher, with the aim of obtaining a complete set of historical documents relevant to this issue. Searches were performed for any documents which referred to 'hormone pregnancy tests', 'hormonal pregnancy tests' or to any of the 12 branded products known to be used as an HPT. In total 151 files were ordered and reviewed of which 108 files contained no relevant information. Of those that contained relevant information, 32 files were copied partially and 6 were copied fully. These are summarised in the tables in Annex F and are available on the CHM website.

b) Joint Standing Committee on Proprietary products (the 'McGregor Committee') (1967 - 1971)

Sodium Valproate

Sodium valproate was not considered by the Joint Standing Committee on Proprietary Products as a licensing application for valproate was not received until 1971, with committee consideration taking place at the Committee on Safety of Medicines in 1972.

Hormone Pregnancy Tests

We have minutes dated 1965 from the Standing Joint Committee on Classification of Proprietary Preparations (TNA ref MH 149/23). They describe the application and approval of Provera, the evaluation of which concluded that since it never causes withdrawal bleeding in pregnancy, it can be used as a pregnancy test. The National Archives also holds MH 149/730 relating to the Standing Joint Committee on the Classification of Proprietary Preparations: minutes of meetings and working papers for the period 1967 Jan 1 - 1968 Dec 31.

25) Given that patient awareness of the risks of valproate use during pregnancy is low, what actions are you taking to ensure that the pregnancy prevention plan is communicated to the target groups? How are you checking the effectiveness of communication?

We accept that patient awareness of the risks of valproate use during pregnancy is low and are undertaking a range of actions urgently to address this, building on stakeholder work we have conducted and liaising continually with the patient groups who are keeping us closely informed of the patient perspective.

While patients' awareness is central to achieving harm reduction, successful implementation of the valproate Pregnancy Prevention Programme requires actions across the healthcare system to ensure that women on valproate are identified, have their treatment reviewed, are supported to understand the risks of valproate in pregnancy and are on effective contraception if valproate is the only effective medicine for them and they need to remain on treatment. The main target groups for our communications have therefore been the healthcare professionals – specialist prescribers, GPs and pharmacists – who need to take action.

On 24 April 2018, a letter was sent from the Chief Medical Officers across the UK to inform healthcare professionals of the new restrictions to the marketing authorisation for valproate-containing medicines relating to the introduction of the pregnancy prevention programme (PPP) and a Written Ministerial Statement was made to Parliamentarians. The CMOs' letter asked all healthcare professionals to respond to the new measures which introduced a contraindication in women of childbearing potential unless they meet the conditions of the PPP. The nationally agreed materials supporting the PPP were published online at the same time and prepared in hard copy for distributions to prescribers and dispensers of valproate by the marketing authorisation holders. This hard-copy distribution was expected to be fully complete by August 2018.

This communication has subsequently been reinforced by articles in the April, May and September editions of Drug Safety Update (DSU) which is sent to over 140,000 healthcare professionals including GPs, practice managers and hospital doctors. Post-publication DSU alerts were also sent to the following key providers of information in order for them to disseminate to their audiences: British National Formulary (BNF), Dispensing Doctors' Association, General Pharmaceutical Council, Monthly Index of Medical Specialities (MIMS), NHS Choices, NICE, pharmacy professional bodies and relevant Royal Colleges.

Following on from the CMO's letter in April 2018, and in order to support the introduction of the new materials, MHRA undertook the following wider communications: a press release that included 18 supportive quotes from key stakeholders was sent to selected media including the BBC and the Press Association; social media messaging was used to target women or girls who follow epilepsy or similar campaigns and blogs on Facebook and Twitter, plus healthcare professionals on LinkedIn; VSN organisations sent supportive communications and social media messages to their members and supporters.

The press release was picked up in mainstream media by the BBC, Independent, The Sun, Daily Mail, ITN, ITV, Sky News Channel 5, Channel 4, Metro, Evening Standard, Reuters, and EuroNews. It was also featured in industry/trade publications including 'The Pharma Letter', 'Pharmafocus', 'British Medical Journal', 'Pharmaceutical Journal'. We estimate that the print media alone had a combined public reach of six million people.

The social media effort at the time resulted in: 49,023 impressions (number of times message has been seen by an individual user), 218 shares, 293 likes. We subsequently undertook a paid-for social media campaign which reached over 190,000 people on Facebook (72% of them were women) and 254,000 people on Twitter. 14,000 people were

reached on LinkedIn, with 416 of those clicking through for further content. Since April 2018 the valproate content on MHRA's GOV.UK website pages have been viewed 34,645 times by 23,893 unique individuals.

In 2016 MHRA established the Valproate Stakeholder Network (VSN). The VSN is currently composed of representatives from over 40 different organisations including: healthcare professional bodies, health system delivery agencies and regulators, patient groups and research charities (for the indications of bipolar, epilepsy and migraine) plus patient groups representing the families affected. The purpose of the VSN is to provide stakeholders with opportunities to input to the development of the materials to support implementation of the new regulatory measures and to assist the dissemination of the information, to healthcare professionals and patients, through their own networks and communication channels. Following the message from the CMOs, the VSN has met on 7 May and 25 July 2018 to review collectively the impact of the communications and identify any barriers to implementation which need to be addressed. A smaller group of clinical leads has also met to discuss what further actions are needed.

The VSN has provided valuable input into the content and presentation of the materials used to raise awareness of the risks associated with the use of valproate during pregnancy. The VSN has highlighted various barriers to successful implementation which have now been addressed. These included ensuring all of the relevant healthcare professional groups were targeted in communications and the problem of pack splitting which resulted in some patients receiving their medication in white boxes without any of the approved warnings or the patient information leaflet. We have requested the manufacturers to produce smaller pack sizes to ensure that patients receive valproate in the original packaging bearing the warning and pictogram and containing the patient information leaflet. All products will be supplied in appropriate pack sizes from November 2018 once manufacturing changes have been implemented. However, for those patients who are still dispensed split packs, additional stickers have been provided to pharmacists to ensure those patients also receive the warning.

As a result of patient groups providing evidence that the statutory patient information leaflet was not being provided with valproate supplied in white pharmacy boxes, the MHRA and four Chief Pharmaceutical Officers wrote to pharmacists on 22 October 2018 emphasising that all dispensed medicines containing valproate should be accompanied by a statutory patient information leaflet.

To ensure that GPs are aware of the new restrictions and have the tools to identify women in their care on valproate, we worked with NHS Digital to require all GP prescribing systems to be updated with demographically targeted alerts which flash up when a female aged between 14 and 49 is prescribed valproate. The GP systems suppliers also provided a search and audit tool to enable GPs to easily identify relevant patients.

In collaboration with the Royal College of GPs and the Royal Pharmaceutical Society we produced a video animation in 2017 to help raise awareness of the 'valproate toolkit' amongst GPs and pharmacists. This year we worked again with both organisations, plus the Community Pharmacy Patient Safety Group, to produce an updated version to support relevant healthcare professionals in implementing the new 2018 regulatory measures, including the PPP and regular patient reviews. Since going live in August 2018, the video has been viewed over 1,600 times. The previous version had a similar total number of views but over a twelve-month period.

We have worked with the national network of Medicines Safety Officers (whose key role is to promote the safe use of medicines across their organisations and be the main experts in this area) to facilitate the implementation of the PPP and to check effectiveness of communications.

We have worked closely with the Devolved Administrations to ensure that measures are implemented UK wide.

We have taken opportunities provided by meetings of healthcare professionals and patients bodies to disseminate information. MHRA has had a speaking slot or a stand or one planned at the following events:

- Association of British Neurologists Annual Meeting
- INFACT Valproate Conference
- National Association for Patient Participation Conference
- Primary Care Pharmacy Association Annual Conference
- School & Public Nurses Association Conference
- Royal College of Psychiatrists International Congress
- Epilepsy Specialist Nurse Association Annual Conference
- Patient Safety Congress
- International Pharmaceutical Federation Conference
- Royal College of Midwives Conference
- Royal College of General Practitioners Annual meeting
- Royal Pharmaceutical Society Wales Medicines Safety Conference

The total audience size across all of the above events attended, according to organisers' estimates, was at least 14,000 healthcare professionals in primary care and specialist roles.

On 21 August the patient organisation INFACT raised concerns about compliance with the PPP based on the results of an online survey of 73 women and video recordings of women who had not received the PPP materials. We have met with INFACT to review their survey results and the evidence that they have of instances of lack of compliance with the PPP. We are undertaking further investigation of these instances. However, some individuals may not have received the materials due to the ongoing distribution of hard copies of the materials at the time of the survey. INFACT are planning to repeat their survey and this will help to inform us on the on-going effectiveness of the communication and whether any further action is required.

We have written to the General Medical Council, the General Pharmaceutical Council and the Care Quality Commission to ask them what action they propose in the light of the concerns raised. We have also published an article in our September Drug Safety Update electronic bulletin to inform healthcare professionals that they should now be ensuring that women on valproate have received the information and appropriate specialist referral.

The effectiveness of the communication, in terms of its impact on practice, is also being explored through the monitoring of the implementation of the Pregnancy Prevention Programme.

26) How are you monitoring implementation of the pregnancy prevention plan? Please clarify the position of a woman with epilepsy who understands the risks and still wishes to become pregnant while using sodium valproate?

The MHRA is actively monitoring the impact and effectiveness of the valproate Pregnancy Prevention Programme (PPP) and its implementation in substantially reducing prescribing of valproate in females where alternatives are effective, and in eliminating exposures during pregnancy through a number of routes which are being brought together to help understand the different aspects of the plan. The MHRA has regularly sought advice from the CHM's Expert Working Group on Valproate on the plans and activities to monitor implementation of the valproate PPP and the data from these activities as they become available.

The main approach being undertaken by the Agency is through the use of routinely collected data on prescribing and use during pregnancy from the Clinical Practice Research Datalink (CPRD), NHS Business Services Authority (BSA), and NHS Digital. This monitoring which is happening on a quarterly or 6-monthly basis depending on the data source, and was started several years ago, is tracking the rate of prescribing of valproate to women across different age groups and disease areas, the rate of new initiations of treatment, and use specifically during pregnancy. The latest data from NHS BSA on prescribing in women and girls in England in the community can be found here. This shows a gradual decline in usage of valproate among women and girls and supports the trends seen in the CPRD data.

The CPRD is currently being used by the MHRA to look specifically at valproate prescribing in pregnancy[27] while exploratory work to understand how NHS Digital's Hospital Episode Statistics data can be linked to NHS BSA prescribing data to scale this up to a national level is undertaken. Similar work is also ongoing in the Devolved Administrations.

The originator MAH, with supporting financial contributions from other MAHs, is conducting a wider study including in other European countries. Interim results suggest that in most cases across the five countries, there was no other epilepsy medication tried prior to the prescription of valproate. The valproate risk minimisation measures will be included in audits being conducted by the Royal College of Psychiatrists and the Royal College of Paediatrics and Child Health and the MHRA is working with these organisations to ensure any data arising from them are available for wider monitoring of the Pregnancy Prevention Programme.

The MHRA is designing a registry together with input from relevant experts that will aim to monitor all females prescribed valproate. While there was no requirement placed on the Marketing Authorisation Holders by the European Medicines Agency following the EU referral, this is considered important from a UK public health perspective given national implementation of the pregnancy prevention programme. Advice from the CHM's Expert Working Group on Valproate is being sought and we will collaborate with relevant healthcare organisations through the Valproate Stakeholder Network. Regulatory experience shows us that broad established academic-led registries generally provide much richer data that drug-specific industry led registries and so such input is necessary[28]. Once initial advice has been obtained, the MHRA will make recommendations on the scope and design of the registry and associated costs and timelines and support plans for implementation.

Surveys will also be conducted by the Marketing Authorisation Holders and the Agency, in collaboration with a number of Epilepsy charities, in addition to those conducted by the patient organisation INFACT, to help identify changes in the level of knowledge and

[27] Dellicour S, Campbell J, Coton S, and Donegan K. Utilising the CPRD pregnancy register to examine the pattern of antiepileptic drug use during pregnancy in the United Kingdom. Pharmacoepidemiology and Drug Safety, 2018. p381. Drug Safety, 2016; 27(S2); p39.

[28] Bouvey JC, Blake K, Slattery J, De Bruin ML, Arlett P, Kurz X. Registries in European post-marketing surveillance: a retrospective analysis of centrally approved products, 2005-2013. Pharmacoepidemiology and Drug Safety, 2017: 26; p1442-1450.

understanding of patients and healthcare providers of the risks and the new risk minimisation measures. The MHRA has ensured that the communications required from the Marketing Authorisation Holders for valproate to pharmacists have been distributed to all UK pharmacies. Several pharmacy professional organisations are also conducting surveys and audits within community pharmacies about the requirements on pharmacists in the implementation of the Pregnancy Prevention Programme and other risk minimisation measures and they will feedback on findings to the MHRA Valproate Stakeholders Network.

The use of valproate by a woman who wished to become pregnant (and therefore was openly, to the knowledge of the treating clinician, not following a Pregnancy Prevention Programme) would be outside the terms of the medicine's licence. Any such decision would be a matter for an individual patient and their specialist(s). As an off-label prescription, the prescriber would need to take responsibility for, and record the reasons for, that decision: in this regard, there is relevant GMC guidance on any clinical decision to prescribe medicines outside the terms of the product licence. Such a decision may well give rise to a risk of liability issues for the prescriber in the event of an adverse outcome, the nature of which would depend in particular on the individual circumstances of the patient and the reasons for the prescriber's decision.

If the patient herself was counselled about the risks, was able to obtain a prescription and wanted to become pregnant whilst taking valproate (whether by refusing to participate in a Pregnancy Prevention Programme, or not following it even if in place), there would be no regulatory basis on which the MHRA could intervene. Issues relating to professional conduct and/or civil liability of the prescribing doctor, or of the patient in relation to any harm to her unborn child, fall outside the scope of the MHRA's regulatory remit.

27) With specific regard to Levetiracetam and gabapentin, how have lessons learnt from valproate medications been applied to testing and guidance for newer anti-convulsant medications?

The lessons learnt from thalidomide and other teratogens have meant that testing and guidance for new medicines which may be teratogens, including anticonvulsants, is a regulatory priority, and guidance is kept up to date as new approaches become available. The potential for reproductive and developmental toxicity of new medicines is assessed in animal studies during development as described in ICH guidance M3 and S5. These studies can identify a range of effects including malformations and fetal toxicity. The studies also evaluate the potential for adverse effects on the long-term development of off-spring following maternal exposures and include an assessment key developmental markers and effects on behaviour. If potential risks are recognised at the time of licensing, clear warnings are included in the SPC and patient leaflets. The risks are also considered as part of the risk management plan and appropriate measures taken to minimise and carefully monitor the potential risks.

Monitoring the safety of medicines is an ongoing process with continuous lessons learnt from experience. Data evolves and changes with time and the MHRA is committed to reviewing new data as it emerges to ensure patients and prescribers receive the most up to date information in order to make an informed decision regarding treatment.

The majority of medicinal products or chemical substances administered to a pregnant woman could have effects on the foetus either before the placenta is fully developed or subsequently, if they can cross the placenta to at least some extent. Substances used for therapeutic purposes in the mother have the potential to reach the foetus with the consequential potential for harmful effects, depending on whether the rate and extent of drug transfer results in sufficient concentrations within the foetus.

Medicinal products may have a different impact at different stages of pregnancy. The spectrum of effects varies according to the period of exposure. For example, the exposure to a teratogenic agent during the period of organogenesis may induce major malformation, growth retardation or death, while exposure during the second or third trimester may induce growth retardation, renal insufficiency, neurological disorders, stillbirth, etc.

Drug treatment of male patients prior to or around the time of conception and/or during pregnancy could affect the offspring due to a drug-induced defect in the spermatozoon itself such as an effect on the DNA or chromosome or due to an effect caused by the presence of the drug in the seminal fluid.

In order to optimise the knowledge about any potential teratogenic or embryotoxic/foetotoxic effects of a medicinal product and the doses and concentrations at which such effects will develop, it is desirable to gather information about all medicinal products taken by pregnant women.

There is guidance on how to monitor accidental or intended exposure to medicinal products during pregnancy and specific requirements for reporting data and adverse outcomes of pregnancy exposure.

The possibility of transmission of the adverse effects of valproate through different generations via transfer of altered genetic material was introduced to the recent EU Referral by the scientific report in Nature by Choi et al (2016)[29] which reported observed transgenerational transmission of autism-like symptoms and increased expression of excitatory postsynaptic proteins in mice after paternal exposure.

[29] [1] Choi, C. S. *et al.* The transgenerational inheritance of autism-like phenotypes in mice exposed to valproic acid during pregnancy. *Sci. Rep.* **6**, 36250; doi: 10.1038/srep36250 (2016).

A multidisciplinary panel of experts to explore the potential impact of valproate on the sperm epigenome, and its potential consequences for offspring is being convened by the EMA. The panel will help shape strategy, design studies and identify laboratories to conduct studies.

The feasibility of conducting a retrospective study using existing Real-World data sources to evaluate whether paternal exposure to valproate at the time of conception is associated with an increased risk of Autism Spectrum Disorders (ASD) in offspring is also being investigated within the European Medicines Agency.

To perform such a study, the Real-World data sources will need to meet the requirements as follows:

- the link between the childrens' and parents' health data, including medication exposure, the exact start date of pregnancy, and the offspring outcomes;
- a longitudinal follow-up of the children to at least 6 years of age; and
- a large number of parent-child pairs to allow for an analysis with sufficient power since the exposure to valproate is estimated to be less than 1% (in the general population) and the frequency of outcomes of interest in children lower than 2%.

The proposal for studies using Real World data was endorsed by the Pharmacovigilance Risk Assessment Committee (PRAC) and the manufacturers have been asked to expand the analysis to include other neurodevelopmental disorders in addition to Autism Spectrum Disorder.

Work is ongoing at EU level on a Good Vigilance Practice guidance for marketing authorisation holders and competent authorities on how to strengthen signal detection and collection of long-term data to follow up any children exposed to antiepileptics and to monitor their development.

Levetiracetam was issued a centralised marketing authorisation by the European Commission in 2000. The European Public Assessment report outlines the data on which the authorisation was issued, including the results of clinical studies and studies in animals. Since licensing, the safety of levetiracetam in pregnancy has been monitored using prospective registries. The latest cumulative re-evaluation of data from 3 separate registries on pregnant women exposed to levetiracetam monotherapy (more than 1800, among which in more than 1500 exposures occurred during the 1st trimester) does not suggest an increase in the risk for major congenital malformations. These data are not sufficient, however, to completely exclude a teratogenic risk.

Only limited evidence is currently available on the neurodevelopment of children exposed to levetiracetam monotherapy *in utero*. However, available epidemiological studies (on about 100 children exposed *in utero*) do not suggest an increased risk of neurodevelopmental disorders or delays.

The current guidance in the Summary of Product Characteristics for levetiracetam is as follows, based on an update agreed by the Pharmacovigilance Risk Assessment Committee following review of data from registries:

"Women of child bearing potential

Specialist advice should be given to women who are of childbearing potential. Treatment with levetiracetam should be reviewed when a woman is planning to become pregnant. As with all antiepileptic medicines, sudden discontinuation of levetiracetam should be avoided as this may lead to breakthrough seizures that could have serious consequences for the woman and the unborn child.

Monotherapy should be preferred whenever possible because therapy with multiple antiepileptic medicines AEDs could be associated with a higher risk of congenital malformations than monotherapy, depending on the associated antiepileptics.

Pregnancy

A large amount of postmarketing data on pregnant women exposed to levetiracetam monotherapy (more than 1800, among which in more than 1500 exposure occurred during the 1st trimester) do not suggest an increase in the risk for major congenital malformations. Only limited evidence is available on the neurodevelopment of children exposed to Keppra monotherapy in utero. However, current epidemiological studies (on about 100 children) do not suggest an increased risk of neurodevelopmental disorders or delays.

Levetiracetam can be used during pregnancy, if after careful assessment it is considered clinically needed. In such case, the lowest effective dose is recommended.

Physiological changes during pregnancy may affect levetiracetam concentration. Decrease in levetiracetam plasma concentrations has been observed during pregnancy. This decrease is more pronounced during the third trimester (up to 60% of baseline concentration before pregnancy).

Appropriate clinical management of pregnant women treated with levetiracetam should be ensured.""

Gabapentin was originally authorised in the UK in 1993. In 2004 was subject to a European referral to ensure consistent advice was provided to healthcare professionals and patients across Europe. Details of the referral are here. The current guidance in the Summary of Product Characteristics for gabapentin in relation to use in pregnancy is as follows:

"Pregnancy

Risk related to epilepsy and antiepileptic medicinal products in general

The risk of birth defects is increased by a factor of 2 – 3 in the offspring of mothers treated with an antiepileptic medicinal product. Most frequently reported are cleft lip, cardiovascular malformations and neural tube defects. Multiple antiepileptic drug therapy may be associated with a higher risk of congenital malformations than monotherapy, therefore it is important that monotherapy is practised whenever possible. Specialist advice should be given to women who are likely to become pregnant or who are of childbearing potential and the need for antiepileptic treatment should be reviewed when a woman is planning to become pregnant. No sudden discontinuation of antiepileptic therapy should be undertaken as this may lead to breakthrough seizures, which could have serious consequences for both mother and child. Developmental delay in children of mothers with epilepsy has been observed rarely. It is not possible to differentiate if the developmental delay is caused by genetic, social factors, maternal epilepsy or the antiepileptic therapy.

Risk related to gabapentin

Gabapentin crosses the human placenta.

There are no adequate data from the use of gabapentin in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Gabapentin should not be used during pregnancy unless the potential benefit to the mother clearly outweighs the potential risk to the foetus.

No definite conclusion can be made as to whether gabapentin is associated with an increased risk of congenital malformations when taken during pregnancy, because of epilepsy itself and the presence of concomitant antiepileptic medicinal products during each reported pregnancy."

It is vital that prescribers and women have access to the most up to date advice based on the best available data of use of medicines in pregnancy in order that they can make informed decisions about their treatment. There is good evidence from observational studies and registries[30] that the risks of valproate of both physical and neurodevelopmental disorders are greater than those of other antiepileptics. Valproate is the only anti-epileptic to currently have a formal Pregnancy Prevention Programme. The regulatory position with other antiepileptics reflects the current knowledge on their risks during pregnancy. This is updated as new evidence emerges from spontaneous reporting, observational studies or registries.

[30] Refs

Weston J, Bromley R, Jackson CF, Adab N, Clayton-Smith J, Greenhalgh J, Hounsome J, McKay AJ, Tudur Smith C, Marson AG. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Database of Systematic Reviews 2016, Issue 11. Art. No.: CD010224. DOI: 10.1002/14651858.CD010224.pub2

Meador KJ1, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, Kalayjian LA, Kanner A, Liporace JD, Pennell PB, Privitera M, Loring DW; NEAD Study Group.

Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol. 2013 Mar;12(3):244-52. doi: 10.1016/S1474-4422(12)70323-X. Epub 2013 Jan 23.

Bromley R. The treatment of epilepsy in pregnancy: the neurodevelopmental risks associated with exposure to antiepileptic drugs. Reproductive Toxicology 64 (2016) 203-10

28) Please can you describe the governance process around the Expert Working Group on Hormone Pregnancy Tests?

The governance process for the Expert Working Group on Hormone Pregnancy Tests followed the requirements set out in the Human Medicines Regulations 2012 (Part 2) on the CHM and its expert advisory groups, whereby:

i. the Minister, as the Licensing Authority, directed the CHM as the 'advisory body' to appoint an expert advisory group in the form of the Expert Working Group on Hormone Pregnancy Tests, to conduct a review;

ii. the CHM was consulted on the draft terms of reference for the Group and the membership, and appointed Dr Gebbie as the Chair;

iii. the EWG conducted the review, reached recommendations as set out in its report and provided its advice to the CHM;

iv. after careful consideration of the report the CHM fully endorsed its conclusions and recommendations and gave its advice to the Minister; and

v. the report was published in the House, accompanied by a Written Ministerial Statement.

Treatment by MHRA of members of the Association for Children Damaged by HPTs

An issue for which MHRA has been criticised relates to the perceived poor treatment of members of the Association by MHRA, leaving them feeling distressed or disappointed. Specific criticisms included feeling rushed when presenting their personal experiences to the EWG and being asked no questions by the Group.

In recognition of the fact that this could be an intimidating experience for the members, and was not something MHRA had done before, much dialogue between October 2015 and the meeting in December was held between MHRA and the Chair of the Association for Children Damaged by HPTs (Mrs Lyon) to try to help the Association members provide an account of their experiences with the least possible amount of stress or upset. During these discussions:

- the MHRA's Patient and Public Engagement Group offered to provide help and support to those attending the meeting, in advance and on the day;
- the MHRA asked Mrs Lyon if she had any specific guidance for MHRA, given this could be a daunting experience;
- the MHRA requested whether any members had any specific requirements (other than wheelchair access) we needed to be aware of;
- the MHRA asked what members' preferences were for talking to experts, and whether they would prefer to be seated around the table and whether they would want to all be present in the room at the same time;
- Mrs Lyon confirmed that members would prefer to speak with the EWG individually and that they would have approximately 15 mins;
- Mrs Lyon told members to arrive for 11am and that the EWG would likely be ready to speak with them at around 12-ish;
- MHRA asked if the members would prefer to wait in a private room before speaking to the EWG;
- MHRA predicted that the EWG may be ready to talk to members from 11am;

- A private room and refreshments were made available;
- Mrs Lyon was informed that there would be space at the end of the room so that people could choose to talk to the Expert Working Group from the lectern or to stay seated at the table (whichever they would find more comfortable);
- A guidance document about the review and what to expect on the day was provided to Mrs Lyon and the members; and
- Four members of staff were made available to assist and escort members on the day,

On the day, the Chair of the EWG told each of the members to take as much time as they needed, and experts were asked if they had any questions for the members after each presentation. A detailed log of the meeting suggests that members generally took five to six minutes to recount their stories (ranging from one to eight minutes) and were asked an average of three questions by the EWG.

In view of the unintentional distress felt by the families, the MHRA has reflected on this experience and will ensure that the instructional information supplied to attendees ahead of any similar events in future is reviewed to ensure that it explains as clearly as possible the nature of the meeting, how it will be conducted and what to expect. Sufficient time would also be dedicated to listening to the experiences of individuals who attend an expert group to ensure no one felt pressurised or let down.

29) Please can you provide copies of the Product License of Right applications for all of the products which had previously been marketed as hormone pregnancy tests.

The Product Licences of Right (PLR) are provided as separate files (see 'Product Licences of Right for Q29.zip') for:

Primodos

Amenerone

Amenorone Forte

Paralut Forte Injection

Paralut Forte Tablets

Paralut Injection

Paralut Tablets

We do not hold the PLRs for Disecron, Menstrogen, Orasecron, Pregornot, Norlestrin, Aorlestrin-A, Primodos injectable, Secrodyl and Norone.

ABDOMINAL AND VAGINAL PELVIC MESH QUESTIONS

30) We recognise that the majority of patients will not have any follow-up actions providing their implanted device functions well. For patients who experience adverse events, roughly what proportion are reported to clinicians and/or MHRA? What could we do to improve the adverse event reporting process?

Academic research has tried to determine the true number of patient safety incidents compared to the number that are reported. This proportion comes out at around 10%, with a variety of determinants of higher or lower proportion, including immediacy, severity, salience, habit etc. This is fairly consistent over a range of patient types, staff types and illness and procedure types, so is not specific to mesh. It is however sensitive to the definition of patient safety event, which is again different to adverse event, critical event, complication and defective device. As noted in our answer to question 4, a retrospective collection of the clinical findings at explant undertaken for a different implantable medical device, the PIP breast implant, revealed that 1 in 6 of implant ruptures were reported to MHRA's reporting systems (Paragraph 23, Page 11). We have not done any further studies in the medical device area.

As also noted in the Howe Review (PIP; review of the actions of the Medicines and Healthcare products Regulatory Agency (MHRA) and Department of Health) adverse incident reporting has some limitations. It relies upon all those involved in delivering care - clinicians, healthcare providers and manufacturers - playing their part in full and acknowledging the importance of adverse incident reporting in protecting patient safety. For a brief outline of how we have been improving the reporting process of adverse incidents see Q2.

It is important to know we do not assign blame or liability associated with adverse events we receive from users.

In response to Q1 mesh timeline for 2017, we have provided a progress update on raising awareness of reporting events relating to mesh.

We also outline below our initiatives to improve our knowledge of post market experience with all medical devices:

A) From Healthcare professionals:

- worked with NHS Improvement (NHSI) to develop a network of Medical Devices Safety Officers (MDSOS) and their counterparts Medications Safety Officers (MSOs). These individuals are in NHS organisations and have responsibilities to promote adverse incident reporting within their organisations and to disseminate safety messages to promote patient safety (see response to Q7 and Q8 for safety messages). We have jointly held with NHSI, well attended conferences for MDSOs/MSOs to share experience and best practice.
- brought devices adverse incident reporting under the Yellow Card Scheme as a means of increasing awareness of the importance of reporting adverse incidents with medical devices.
- worked with the General Medical Council (GMC) to incorporate an obligation in their Ethical Guidance on 'Prescribing and managing medicines and devices' to report adverse incidents involving medical devices to national bodies including MHRA
- worked with professional bodies and Royal Colleges to promote reporting.
- undertaken research to explore how we can increase adverse incident reports from community health care professionals such as district nurses, GPs etc. This insight work will inform future campaigns to increase adverse incident reporting.

- been working with NHSI in the development of the patient safety incident reporting system (DPSIMS) this system will eventually replace the National Reporting and Learning System (NRLS). The purpose of this project is to introduce a single reporting system for patient safety incidents. The advantage of this system is that healthcare professionals will need to register an incident only once and the details of this incident will be logged with their organisation and with all interested parties e.g. NHSI and MHRA. Also see responses to Q2, Q6 and Q9.
- been working with Scan4Safety pilot sites (see response to Q31) to encourage the use of GS1 Unique Device Identifiers (UDIs) in electronic patient records enabling the real time link between person, place and use of the device.
- explored Clinical Practice Research Datalink (CPRD) as well as NHS England and NHS Digital as options for using existing NHS data sources to detect earlier and better signals via machine learning. We are also keen to explore options such as extending the Scan4Safety initiatives to all healthcare providers.
- We are currently developing a common reporting standard (a cutdown version of the manufacturer reporting standard described below) with NHS Digital to receive high quality reports from healthcare establishments and for feedback of safety information. This will be similar in concept to the medicines reporting standard (E2B). Once developed we plan to promote its integration it into all relevant healthcare systems to facilitate reporting, especially local risk management systems and GP systems e.g. DPSIMS, EMIS, Datix, Ulysees etc.

B) From Manufacturers - by driving forward improvements as follows:

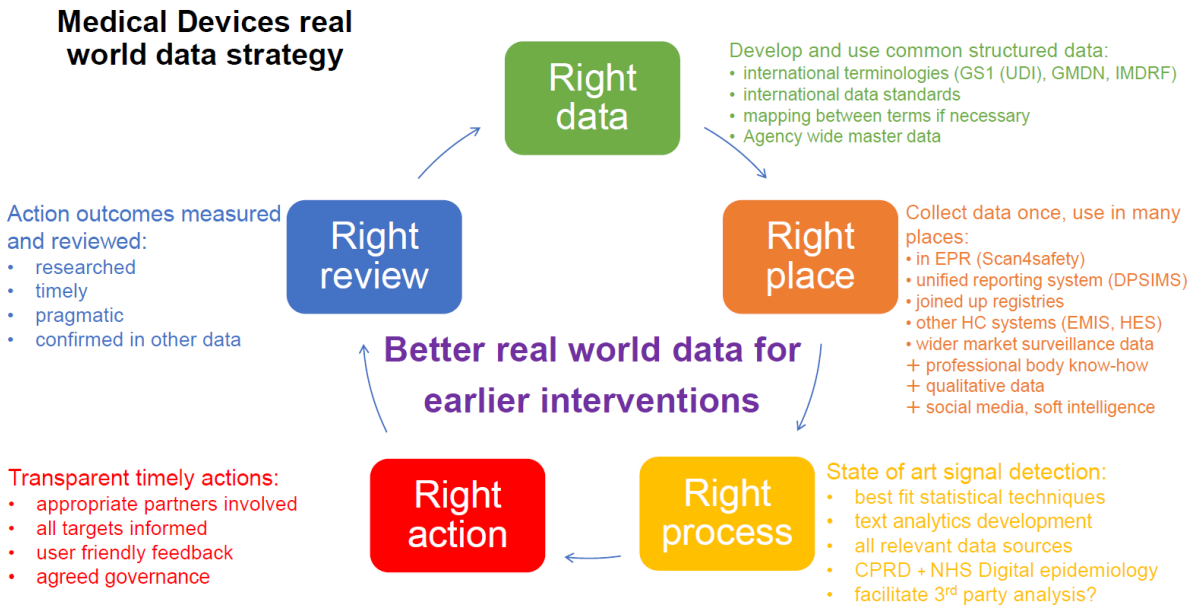
- Redesigning the European manufacturer reporting form to include
  - New global adverse event terminology for what went wrong, why (root cause) and actions taken.
  - Introduction of unique device identifiers (UDI).
  - Similar incident data for UK, Europe and Worldwide together with its appropriate denominator data.
  - the common reporting standard for automatic two-way exchange of adverse incident information.
- Redesigning the European Field Safety Notice (FSN) for better communication of learning from adverse events (see response to Q7 and Q8).
- Leading the design of the first medical device Periodic Safety Update Report (PSUR) and its associated guidance to facilitate the implementation of the forthcoming Medical Device Regulations. This will provide helpful summaries of all manufacturer post market surveillance activities for higher class medical devices. Also see response to Q20.

While the Howe Review encouraged everyone involved to redouble their efforts to improve reporting and ensure that information is shared with the MHRA, reporting will never reflect 100% of the experience with a device and this means other information must be generated and used (as demonstrated in response to Q1 timeline for mesh).

The MHRA must be able to obtain evidence from a wider and more detailed set of sources, including robust outcomes data from clinicians. A significant issue when reviewing evidence is the quality of the data held in any information source. This is just as, if not more important than the quantity of data. For example, HES data can be sometimes be used as an indicator of complication rates, but it is not equivalent to medical device adverse incident reports where the particular device involved is identified and a full description of the incident is

provided. Examples of other information used would include well designed registries and real-world data. Also see response to Q2.

We have sought to be at the forefront of using more sophisticated and rich sources of data to determine if there are problems with a device. This is evidenced by our wide post market surveillance strategy as outlined in our medical real-world data strategy, see illustration below.



31) What mechanisms are in plan for tracking the usage of medical devices in both the public and private sector? How could device traceability be improved? What technology would need to be in place to enable this? How would a registry assist with this process?

Several measures are in place (or planned) to improve the tracking of the use of medical devices. These include:

- the introduction of the Scan4Safety demonstrator pilot in England;
- requirements for manufacturers/hospitals to provide implant cards to patients who receive implantable medical devices; and
- the use of Unique Device Identification (UDI) in safety communications.

Scan4Safety

The following response was prepared in collaboration with the DHSC Scan4Safety team. The Scan4Safety programme is designed to enable the track and trace of medical devices in NHS acute hospitals in England by using global standards, commonplace in retail and aerospace industries, to uniquely identify patients, products and places and implementing common processes.

In its most tangible application, this involves the use of barcodes to track and trace medical devices from manufacturer to point of care, using standardised barcodes based on internationally recognised standards (GS1).

The Department of Health and Social Care (DHSC) has mandated acute NHS trusts in England to implement GS1 standards through the NHS eProcurement Strategy, published in 2014, with the aim of improving patient safety, increasing clinical productivity and supply chain efficiency. These standards are mandated for use in the NHS by *the NHS Standard Contract between Commissioners and Providers* and are mandated for suppliers to the *NHS by the NHS Terms and Conditions of Contract for the Purchase of Goods and Services*.

Since 2016, Scan4Safety has been implemented in six acute NHS trusts in England (so called ‘demonstrator sites’). These are:

- Leeds Teaching Hospitals NHS Trust
- North Tees and Hartlepool Hospitals NHS Foundation Trust
- Royal Cornwall Hospitals NHS Trust
- Salisbury NHS Foundation Trust
- University Hospitals of Derby and Burton NHS Foundation Trust
- University Hospitals Plymouth NHS Trust

The Secretary of State for Health and Social Care has indicated that he supports its wider adoption across the NHS in England (see speech here). Since this, there have been some indications of Scan4Safety expanding in the NHS, with acute trusts either self-funding the activity or submitting business cases for non-ringfenced funds, such as regional allocations to Sustainability and Transformation Partnerships (STPs).

Scan4Safety has not currently been adopted in Northern Ireland, Scotland or Wales or in the private sector, though there has been significant interest from, and some engagement with the devolved administrations, private hospital groups and international healthcare systems.

To enable this approach, barcode scanners linked to compatible IT systems need to be available at points of care and in device/equipment storage areas in NHS trusts. Additionally, there is a dependency on suppliers to the NHS to adopt the same standards and label their products accordingly. Engagement with suppliers and technology providers has been led by a central Scan4Safety team in DHSC.

There are potential further applications for the Scan4Safety approach that are, as yet, unproven. These include the expansion of 'use cases' to include staff and assets and to widen the scope to community care.

A key output of Scan4Safety is accurate data, relating to patients, products and places involved in care episodes. The potential applications of the resulting data are numerous and include the opportunity to work with national registries to enrich and automate the population of these registries.

The benefits of scanning for patient safety and care has been recognised by the Healthcare Safety Investigations Branch (HSIB) and 'scanning' formed part of the recommendations that were made by the first Healthcare Safety Investigation Branch (HSIB) report.

The requirements Scan4Safety sets on the NHS enables trusts to comply with significant aspects of the EU Medical Device Regulations (MDR) and EU In-Vitro-Diagnostic Device Regulations (IVDR) and will assist the NHS in England to meet the requirements of the EU Falsified Medicines Directive (FMD).

Implant cards

The new EU Medical Devices Regulation (MDR); which apply to mesh) introduce several measures to make sure that medical devices can be traced. One of these is that manufacturers of implantable devices must provide an implant card with specific information to hospitals to pass on to patients who are implanted with that device (see article 18 of the MDR). The information on the card must include: the device name and model; the Unique Device Identification (UDI); lot number and serial number; name, address and website of the manufacturer. The manufacturer must also provide any warnings or specific information that the patient or healthcare professional needs to know, for example how long the device will last.

The use of Unique Device Identification (UDI) in safety communications

MHRA now includes UDI information (if available) in its safety alerts (Medical Device Alerts), so that if there is a medical device recall, or other safety action, the hospital can easily identify affected devices and take appropriate action.

MHRA has also worked with GS1 UK, manufacturers and NHS representatives to produce 'Recommendations on Medical Device and IVD Field Safety Corrective Actions and Recalls using Unique Device Identifiers & GS1 Standards for manufacturers on the best way of including UDI information in their safety alerts.

As UDI is applied to more and more medical devices, these measures will have an increasing positive impact on safety communication to UK hospitals.

How would a registry assist with this process?

Registries can be very useful to identify patients who have implantable devices which are subject to recalls or other safety actions. For example:

- the National Joint Registry list one of its benefits to patients as "helping surgeons quickly decide whether patients need to return to hospital if implant problems are found"; and

- the Breast and Cosmetic Implant Registry identifies one of its main purposes to be "to record the details of any individual, who has breast implant surgery for any reason, so that they can be traced in the event of a product recall or other safety concern relating to a specific type of implant".

32) In cases where device failure occurs across a class of devices, what measures would you recommend to enable this be detected more quickly, effectively monitored and resolved?

We have interpreted this to mean surgical mesh within the scope of this review that regardless of brand, has similar characteristics to other brands such as the materials it is made from.

Once a mesh device is placed on the market to comply with the requirements of the Medical Devices Directive (MDD), the manufacturer must continually monitor the performance of their device, submit vigilance reports to us (within set deadlines) when certain incidents occur involving their device and take appropriate safety action when required. The manufacturer is normally responsible for the investigation of an incident and we monitor their progress. Additionally, we monitor adverse incidents reported though our voluntary Yellow Card Scheme and we strongly encourage reporting by anyone, patient, carer or healthcare professionals. All these reports (anonymised as appropriate) are sent to the relevant manufacturer to feed into the vigilance system.

Furthermore, the new EU Medical Devices Regulation 2017/745 (MDR), which entered into force in May 2017, have introduced more stringent requirements for manufacturers to ensure a high level of patient safety. These include increased scrutiny by Notified Bodies, particularly for higher risk devices like mesh, new standards for clinical evidence and more rigorous vigilance reporting requirements. Also see response to Q20.

In addition, for early detection and timely resolution of potential safety concerns, we:

- Operate a trending review of ongoing series/categories/types of device incident reports for all medical devices including mesh. This means we analyse grouped adverse event data to determine if there is a potential signal for further investigation and escalate if necessary to seek resolution as quickly as possible. This has been in place since 2011. The coding (nomenclature) system we use for mesh allows us to categorise them by the indication of use (stress urinary incontinence or pelvic organ prolapse).
- Review periodic summary reports (PSRs) for agreed failure types associated with use of mesh implantable devices. This is an alternative way to report similar or common, well documented incidents related to the same device or device type in a consolidated way to monitor for trends of known issues.
- Encourage trend reporting by manufacturers. This is an alternative way to report but only when a significant increase in certain types of events occur beyond a defined threshold set by the manufacturer.
- Involve Devices Expert Advisory Committee (DEAC) or call upon an external clinical expert from our Register of Experts to seek clinical advice or to gain further experience of failures in clinical practice.
- Regular engagement with other EU competent authorities and international regulatory authorities to share safety information to facilitate earlier identification of new issues and seek resolution with the manufacturer and/or its Notified Body. Also see response to Q5.
- Anticipate access to Eudamed databank to gain more experience (see Q5).
- Support an initiative called ‘the development of the Beyond Compliance initiative’. Beyond Compliance is a service provided by an independent panel of experts who work with implant manufacturers to assess the relative risk of new products entering the UK market. This service is voluntary for manufacturers and aims to offer

assurance to prospective patients that the novel high-risk devices accepted into the initiative undergo an enhanced level of scrutiny in the early years of their use. Beyond Compliance is currently focused in the field of orthopaedics, specifically joint replacement implants, but may prove to be a useful model applicable in other medical specialties.

To further improve our safety signal detection systems, we would like to improve the quality of data reported and captured (a registry may help with this depending on what data it collects – see response to Q11) and additional resources such as more data scientists and software systems with analytical ability to facilitate early signal detection. Also see Q2 for further information on our ambitions to unify and improve our reporting and detections systems and our 5-year Corporate Plan.

As per other responses, we support the development of a registry by DHSC which can be helpful to collect device performance data and assist with trends and detection of outlier devices.

Work is underway in the EU to implement a new common coding system to improve accuracy of capturing and reporting of device related adverse incidents, so we can pick up signals quicker. Also see response to Q30. This includes device identification by use a Unique Device Identification (UDI) and common systems of device nomenclature. Also see response to Q31.

33) In your expert opinion, are the revised European Medical Device Regulations sufficient, or should more be done, particularly in relation to pre-market testing?

We believe the Medical Device Regulations (2017/745) (MDR) are sufficient, particularly in relation to pre-market testing.

Clinical data for implants will typically not include an evaluation of long-term clinical performance prior to the CE marking process. This is because it is not feasible to run pre-market clinical investigations for the expected lifetime of an implant, given they are meant to be permanent, and often it is not possible or appropriate to carry out randomised clinical trials such as is done with pharmaceuticals.

However, as evidence provided to Parliament by the MHRA in 2012 previously identified, the Medical Devices Directives could be strengthened more when setting out when manufacturers need to undertake pre-market clinical investigations, or to what extent they are able to rely on existing scientific literature and clinical evidence for pre-existing devices. To address this, we have been instrumental in agreeing the new EU Medical Devices Regulations, which entered into force in May 2017 and help to strengthen the regulatory framework. One of the most important changes introduced is to significantly increase the requirements for robust pre-market clinical data, particularly for implantable devices, and ensure manufacturers are meaningfully following their devices in the clinical setting once they have received regulatory approval.

A key change is this MDR introduces new risk classification rules, meaning certain devices will be reclassified into high risk categories, and will require a more stringent assessment. For example, all implantable surgical mesh will be Class III devices, which is the highest risk class. This means these devices will be subject to a higher level of scrutiny in both pre- and post-market surveillance, including the level of clinical evidence required.

For mesh (class III devices), manufacturers will be required to summarise the main safety and performance aspects of the device and the outcome of the clinical evaluation in a document that should be publicly available. This document is known as the summary of safety and clinical performance (SSCP). The SSCP is part of the documentation to be submitted to the notified body (independent certification bodies designated by the national regulator) involved in the conformity assessment and shall be validated by that body. The manufacturer will also be required to state on the label or instructions for use where the summary is available. More information on the content of the SSCP can be found in Article 32 of the MDR.

The MDR also sets more stringent requirements for clinical evaluation and claiming equivalence (see Annex XIV online for further information). The manufacturer will still be expected to show that the device has the same technical, biological, and clinical characteristics, and demonstrate that there is sufficient access to the data relating to devices with which they are claiming equivalence with. For mesh implants and other Class III devices that includes an agreement to access technical documentation for the equivalent device.

The New Regulations also strengthen post-market requirements in the form of a post-market clinical follow-up (PMCF studies) which already exists in the current Medical Devices Directive). This is a continuous process that updates the pre-market clinical evaluation and requires the manufacturer to proactively collect and evaluate clinical data from the use in or on humans of the CE marked device and is intended to answer specific questions relating to clinical safety and performance.

Clinical data obtained from post-market surveillance and during PMCF studies by the

manufacturer is not intended to replace the pre-market data necessary to demonstrate conformity with the provisions of the legislation. However, they are critical to update the

clinical evaluation (see Q34) throughout the life-cycle of the medical device and to ensure the long-term safety and performance of devices after their placing on the market.

Furthermore, following Poly Implant Prothèse (PIP) implant fraud, pre-market assessments, conducted by notified bodies, were strengthened through the EU Joint Plan.

The Action Plan focuses on 4 key areas: the functioning of notified bodies, market surveillance, coordination of vigilance and communication and transparency.

The MDR largely builds on the requirements already established by this Plan, including joint assessments undertaken by the Notified Body. Briefly, each joint assessment comprises a preliminary off-site evaluation of the documentation submitted by the notified body followed by an on-site assessment at the premises of the notified body. The on-site assessment is led by the national designating authority of the Notified Body (e.g. MHRA) and the joint assessment team participates fully in the assessment.

34) When a device is marketed on the basis of equivalence on an existing device, should there be a notification if the originator device is withdrawn from the market? If so, should this be for any withdrawal, or for safety withdrawals?

For all medical devices placed on the market for use, the regulatory process to obtain a CE mark ensures the design and manufacture of a device does not compromise the clinical condition of patients and users. This is demonstrated by obtaining results and critical analysis of the tests and studies undertaken before it can be placed on the market in the UK/EU; including a 'clinical evaluation'. This includes, but is not limited to, a clinical investigation, which is an assessment and analysis of clinical data to verify the clinical safety and performance of the device. Typically, investigations will be required where a medical implant has new design features or uses new materials. Clinical evidence can be generated from several sources including:

- Clinical experience of the medical device or a similar device;
- Published clinical investigations;
- Other studies of similar devices in the scientific literature; and
- Results from of a specifically designed clinical investigation of the device.

Under the Medical Devices Directive 93/42/EEC (MDD), it is possible, in the EU, to use evidence of the clinical data of existing similar devices. However, equivalence of every single similar device to the new device under evaluation must be fully investigated, demonstrated, and described in the clinical evaluation report. This means that the new device needs to demonstrate identical clinical, technical and biological properties to the one(s) it is claiming equivalence with. If any differences are identified, it needs to be clearly demonstrated there is no clinically significant difference in the performance and safety of the devices triggered by the differences between the new device and the device(s) presumed to be equivalent. EU Guidance for clinical evaluation and the demonstration of equivalence can be found here. It places significant demands on the manufacturer when undertaking a clinical evaluation.

The new EU Medical Devices Regulations 2017/745 (MDR) has more stringent requirements for claiming equivalence in the clinical evaluation (available online, see Annex XIV). The manufacturer will still be expected to show a device has the same technical, biological, and clinical characteristics, and demonstrate sufficient access to the data relating to devices with which they are claiming equivalence with. For mesh products, and other Class III devices, that includes an agreement to access technical documentation for the equivalent device.

The withdrawal of a device involves any measure aimed at preventing a device in the supply chain from being further made available on the market. Under the MDD and MDR, there is no requirement that a notification is issued if the originator device is withdrawn from the market (if it was indeed brought to market in the first place) in this situation. However, generally the withdrawal of the original device should be noted in the clinical evaluation process of the "new" device. This would be reviewed, and the manufacturers of the new equivalent device should take the reason for withdrawal into consideration and ensure that it has been addressed in their own device's risk assessment.

We would investigate any "new" equivalent medical devices as a result of adverse incident reports or intelligence indicating a potential problem. Where a recall of a medical device on the UK market is initiated by the manufacturer for safety reasons, they are required to notify us in accordance with the post market 'Vigilance' system. They will issue a Field Safety Notice to customers detailing what the problem is and what actions the user should take. This Notice is published on our website and we closely monitor the customer response and will take action if needed to ensure that the device affected is recalled (also see Q7 and Q8).

35) Mesh can be made from a variety of materials. Is there consensus on differences in adverse events and success of procedure related to material type?

A wide variety of materials have been used in medical devices for tissue repair, from synthetic to biologically derived, non-resorbable to resorbable. Of all the materials that are currently in use for mesh applications, polypropylene is the most common.

Despite being firmly established in its medical use, the biocompatibility and/or safety of polypropylene frequently comes into question and is of concern to some women. As mentioned in the response to Q1, a peer review report titled; 'In vivo response to polypropylene following implantation in animal models; a review of biocompatibility' was accepted for publication. The report compares polypropylene meshes to see if a particular material causes more problems than others. Polypropylene was actually better than other materials. The conclusion of the report says:

"The evidence reviewed shows that polypropylene evokes a less inflammatory or similar host response when compared with other materials used in mesh devices."

It is important to know that there are different procedures for treating stress urinary incontinence (SUI) and pelvic organ prolapse (POP) and different surgical approaches such as transvaginal and abdominal.

The details of the mesh, for example the size of the holes, needs to be different depending where it is being implanted and for which treatment. The type and configuration of mesh that is suitable for treating SUI might not be suitable for treating POP.

The European Commission's Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) published a review in 2015: Opinion on the safety of surgical meshes used in urogynaecological surgery, which included polymers such as polypropylene. It says that type 1 (microporous, monofilament) is "considered to be the most appropriate synthetic mesh urogynaecological use for insertion via the vaginal route", of which several brands of [polypropylene] mesh is included. You will also find a section on page 10-11 of the review on factors that could affect the outcome of surgical procedures which includes route of implantation, patient characteristics, surgeon's experience, as well as material properties and design.

The SCENIHR report is probably the best current overall review of mesh materials for all uses regardless of where in the body it is implanted. Although the title specifies urogynaecology, the content does refer to other uses of mesh.

At the moment MHRA does not have any evidence from the reports of adverse events that mesh made of any one material has more problems when it's used in either procedure to treat SUI or POP. This is because:

- Yellow Card reporting by the public, patients and healthcare professionals is voluntary (it is only mandatory for manufacturers to report to us - see full response to Q22);
- Yellow Card reports are based on device adverse effects or device-related complications or situations where these might happen;
- reports on Yellow Card are not a record of all complications;
- the Yellow Card reports don't always say which type or brand of mesh was used, or what procedure it was used for (sometimes patients don't know this information or have difficulty getting it from their patient records); and
- the report of an adverse event does not mean there is a problem with the device itself.

Regardless of the chosen material, the EU Medical Device Directive and the new EU Medical Device Regulations require the device (including the chosen material) be evaluated for its safety, quality and performance. This includes a biological evaluation (usually to BS EN ISO 10993 series of international standards) to be carried out on the final device after all raw materials have been put together following appropriate processing and never on an individual (unprocessed) material/resin.

For surgical mesh, this will also include following an appropriate assessment by an independent certification body, called a Notified Body, who will issue relevant certification, providing the device meets the requirements set out in the legislation. This allows manufacturers to then put CE marks on their products and sell them anywhere in the EU if they meet the requirements.

Biocompatibility is a complex term and such a risk assessment requires careful consideration of many factors including the type of device, intended condition of use, degree and duration of patient contact and potential of the device to cause harm. It is also important to realise that individual people react differently to the same implant. It is possible for a device to function without problems in one patient but not in another.

We recognise the need for long-term data in this area, so we continue to support the setting up of a registry that can provide valuable large-scale real-world information on the performance of general and specific types of mesh. It would complement other data sources we use for post market surveillance.

We would also like to take this opportunity to respond to the public's concerns of allegations in 2016 of "counterfeit" materials used in urogynaecological mesh used by Boston Scientific.

MHRA took these allegations very seriously. We discussed this situation with other regulators and Boston Scientific. We did review all reported adverse incidents related to urogynaecological surgical mesh and didn't find any evidence that counterfeit materials were used. The products were fit to be used in appropriate treatment pathways.

The USA's Food and Drugs Administration (FDA) posted an update in September 2017 saying that the material used did not present new safety or effectiveness concerns. Their information can be found via this link.

Since this, we are aware of recent media coverage relating to the 2016 [unfounded] allegations of counterfeit raw materials being used in urogynaecological surgical mesh manufactured by Boston Scientific. However, there isn't any new evidence to justify these allegations.

We also understand there have been assertions suggesting urogynaecological mesh can 'shrink', 'twist', 'stick' or 'adhere to organs' after implantation which causes much understandable distress to patients, but there is a great deal of misconception in this regard. Most of these phenomena are related to the host reaction to a foreign body, which is more or less pronounced depending on the individual patient but occurs with any implant. The fibrous tissue which is formed is in part the reason mesh devices used in some procedures is successful, but it is well recognised excessive fibrous tissue, which naturally contracts as scar tissue, may lead to unintended complications in some patients.

These and other complications are reported in manufacturers literature and must, as always, be balanced against the fact they occur in a minority of cases and the serious conditions they are treating, such as urinary and faecal incontinence and external prolapse of the vagina and cervix.

36) Do you have archived minutes from the Devices committee meetings relevant to MHRA publications on pelvic mesh (1996 - present day)?

Yes, we have minutes from Devices committee meetings which are relevant to MHRA publications on mesh.

Surgical mesh has been discussed at several independent expert [committee] meetings, most recently in June 2018.

Committee on Safety of Devices (CSD). Established July 2001:

Before the Devices Expert Advisory Committee (DEAC) was established, we ran the Committee on Safety of Devices (CSD); a committee of independent experts who supported the Agency in ensuring medical devices and equipment meet appropriate standards of safety, quality and performance by giving advice on a range of device related initiatives.

Below are links to published summaries of the meeting's minutes and key points.

- Meeting held on 07 July 2011: Referred to MHRA SUI workshop chaired by Professor Abrams. See full response to Q1 which includes outputs of that workshop.
- Meeting held on 19 July 2012: Recommendations on how we communicate with the public on clinical issues with particular reference to 'vaginal slings and meshes'. See response to Q1 that includes information on our website for patients and clinicians.
- Meeting held on 22 November 2012: Information given including appointing York University to write a report. See full response to Q1.
- Webpages for the CSD are on the National Archives website and can be found here.

Devices Expert Advisory Committee (DEAC)

Further to Professor Terence Stephenson's recommendation for the MHRA to improve its access to clinical advice and engagement with the clinical community, the MHRA set up the Devices Expert Advisory Committee (DEAC) to replace CSD (see response to Q9). It is responsible for providing independent, external expert input and advice on a wide range of aspects relating to medical devices to help the Agency in the execution of its role in ensuring the safe introduction and management of medical devices.

Below are links to summaries of the minutes of the meetings and key points. Other minutes of DEAC meetings can be found here.

- Meeting held on 05 November 2015: The Committee heard a presentation and discussed Transvaginal Mesh Devices.
- Meeting held on 25 February 2016: The Committee was updated on Transvaginal Mesh Devices to treat stress urinary incontinence and pelvic organ prolapse. Further information can be found at: https://www.gov.uk/government/publications/vaginal-meshimplants-summary-of-benefits-and-risks
- Meeting held on 23 June 2016: The Committee was updated on Transvaginal Mesh Devices.
- Meeting held on 02 February 2018: The Committee discussed the latest developments surrounding Transvaginal Mesh implants.
- 07 June 2018 (the summary of minutes is yet to be formally agreed at the November meeting so cannot be provided at time of submission of this evidence. We shall provide this once agreed).

ANNEXES

Annex A: Overview of the MHRA's Role & Responsibilities

Annex B: Detailed Points and a Timeline for Q1 on HPTs

Annex C: Detailed points and a Timeline for Q1 on Abdominal and Vaginal Pelvic Mesh

Annex D: Abdominal and Vaginal Pelvic Mesh Adverse Incident Figures for Q1

Annex E: NICE Interventional Procedures Guidance for Q1

Annex F: Additional Material for Q24

Annex A: Overview of the MHRA's Role & Responsibilities

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WHO WE ARE

The UK's medicines and medical devices regulator is known as the MHRA. The MHRA is a regulatory centre of the Medicines and Healthcare products Regulatory Agency (also known as 'The Agency') which also includes the National Institute for Biological Standards and Control (NIBSC) and the Clinical Practice Research Datalink (CPRD).

The Agency is an executive Agency of the Department of Health and Social Care (DHSC) established on 01 April 2003 and operates as a government trading fund. The Secretary of State for Health and Social Care determines the policy and financial framework within which the Agency operates but is not involved in the day-to-day management.

The Agency's mission is to protect and improve the health of millions of people every day through the effective regulation of medicines and medical devices, underpinned by science and research.

No product is completely free of risk, but sound evidence underpins all the MHRA's decisions to ensure that these risks are minimised.

MHRA RESPONSIBILITIES

The MHRA regulatory centre is responsible for:

- Assessing the safety, quality and efficacy of medicines, and authorising their sale and supply in the UK.
- Carrying out post-marketing surveillance of medicines and medical devices, monitoring adverse reactions and taking action to safeguard public health.
- Operating a separate safety reporting scheme for haemovigilance for the reporting of serious adverse reactions and events related to blood safety and quality.
- Testing medicines to identify and address quality defects, monitoring the safety and quality of imported medicines, investigating internet sales and counterfeit medicines.
- Ensuring compliance with UK and European standards through inspection and enforcement.
- Managing the British Pharmacopoeia (BP).
- Overseeing the UK bodies that audit medical device manufacturers, operating a compliance system for medical devices, and contributing to the development of standards for medical devices.
- Providing expert scientific, technical and regulatory advice on medicines and medical devices.
- Regulating clinical trials of medicines and approving clinical investigations of medical devices.
- Promoting good practice in the safe use of medicines and medical devices, and providing information to help inform treatment choices.

LEGAL FRAMEWORK

- **General**

The Government trading fund that finances the Agency was established by the Medicines and Healthcare products Regulatory Agency Trading Fund Order 2003 (SI 2003/1076), made under the Government Trading Funds Act 1973.

Where the Secretary of State has functions under UK legislation relating to medicines, medical devices and blood, these are performed by the Agency.

The areas in which the Agency operates (including medicines, medical devices and blood) are predominantly the subject of EU legislation, as it applies to and is implemented in the UK.

The current political and negotiating environment around Exiting the EU may change the Agency's work going forward, but currently the Agency's role includes negotiating relevant EU legislation on behalf of the Department of Health and Social Care and implementing that EU legislation in the UK.

Moreover, the regulation of both medicines and medical devices is discharged within an EU-wide legal and operational framework, with an increasingly important role for the European Commission as licensing authority for an increasing range of medicines.

Within the UK, the Agency carries out the functions of the Competent Authority under the various pieces of EU legislation relating to medical products, medical devices and blood regulation. The Agency also actively participates in informal networks in which regulators across the EU exchange experience and discuss implementation of EU legislation; of particular note are the Heads of Medicines Agencies and the Competent Authorities of Medical Devices.

Successfully protecting the public health interests of UK citizens means that the Agency must be an active contributor to these EU-wide regulatory structures and networks for both licensing and vigilance.

- **Medicines**

In the UK, the regulation of medicines is governed by:

• the Human Medicines Regulations 2012 – this replaced most of the Medicines Act 1968 and a large number of orders and regulations;

• the Medicines Act 1968;

• regulations and orders made under the Medicines Act 1968 or the European Communities Act 1972;

• EU Regulations.

The Human Medicines Regulations 2012 implements Directive 2001/83/EC (amongst other things) and is the key piece of UK medicines legislation. The Agency discharges, on behalf of the Secretary of State, the functions that he exercises as the “licensing authority”, “the Ministers”, the “enforcement authority” and the “competent authority” under the Human Medicines Regulations 2012 and other UK medicines legislation.

Medicines is a reserved subject matter as regards Scotland and Wales but transferred as regards Northern Ireland. In relation to Northern Ireland, the Human Medicines Regulations 2012 provides for a single “licensing authority” to issue licences etc, which may act on behalf of either the Secretary of State or the Northern Ireland Health Minister. In practice, by agreement, it is the Agency which performs this function for the whole UK.

- **Medical devices**

In the UK, the regulation of medical devices and *in vitro* diagnostic medical devices is governed by:

- the EU Medical Devices Directive 93/42/EEC (MDD)
- the EU *in vitro* Diagnostic Medical Devices Directive 98/79/EEC (IVDD)
- the EU Active Implantable Medical Devices Directive 90/385/EEC (AIMDD)

These EU Directives are transposed into UK law by the Medical Devices Regulations 2002 (SI 2002 No 618, as amended) (MDR 2002).

Furthermore, two new EU Regulations entered into force on 25 May 2017, namely

- the EU Medical Devices Regulation 2017/745 (MDR) and
- the EU *in vitro* Diagnostic Medical Devices Regulation 2017/746 (IVDR)

A three and five year transition period began on the enter into force date. Therefore, the MDR and IVDR will fully apply in EU Member States from 26 May 2020 and 2022 respectively. During the transition period, devices can be placed on the market under the current EU Directives, or the new Regulations (if they fully comply with the new Regulations).

The changes to the legislation were largely introduced to:

- address the widely varying performance of notified bodies (who carry out pre-market assessment and verify compliance with the relevant essential requirements before the device can be placed on the EU market);
- strengthen the structures for communicating vigilance and post-market surveillance concerns between the Member States, and;
- raise the level of consistency in the way the regulations are interpreted and implemented by the Member States (this is extremely variable due partly to the absence of an effective mechanism to ensure that Member States act on a consensus basis and to inadequate resources being allocated to this area).

The MHRA's powers originate in the Consumer Rights Act 2015, the Consumer Protection Act 1987, and the General Product Safety Regulations 2005, with some light touch powers contained in the UK MDR 2002.

These powers can be categorised as "investigatory" – powers enabling us to acquire information in relation to business activities or specific devices – or "enforcement" – reactive powers to compel compliance with the law and address risks to public health.

GOVERNANCE

The Agency is supported by a non-executive Chair, who is appointed by the Secretary of State for Health and Social Care.

The Chair is supported by an Agency Board comprising the Agency's Chair, together with two Executive Directors (the Chief Executive and Chief Operating Officer) and up to nine Non-Executive Directors, who do not represent any specific customer, sectoral or stakeholder interests and are appointed by the Secretary of State. Other Directors may be invited to attend specific meetings, all or in part, as appropriate.

DHSC is also invited to provide an observer and the Chair may invite observers from the Devolved Administrations. The size of the board and the range of experiences sought from its non-executive members will be agreed between the Agency and DHSC.

The Agency Board collectively does not exercise any line management or executive functions, nor does it have a legal or constitutional role or any liability in respect of decisions of the Executive.

The Agency's Chief Executive is appointed by the Department's Permanent Secretary through fair and open competition in line with the Civil Service Commission Recruitment Principles and chairs the Corporate Executive Team (CET). The CET devolves certain areas of its business to sub-committees, each chaired by a designated director.

The Permanent Secretary nominates a Senior Departmental Sponsor (SDS) who acts as the Agency's designated, consistent point of contact within DHSC.

The SDS acts as the link at executive level between the Agency and the senior officials of DHSC, and also with Ministers. The SDS also supports the Permanent Secretary in holding the Agency to account and providing assurance on its performance. A Departmental sponsor team supports the SDS by undertaking the principal day-to-day liaison between the DHSC and the Agency. The Secretary of State has delegated some of his statutory responsibilities to the Agency.

TRANSPARENCY

Medicines regulation is funded entirely from fees. In setting its fees the Agency takes account of full cost recovery rules as set out in HM Treasury's *Managing Public Money*.

Devices regulation is primarily funded through a service level agreement with the DHSC with approximately 10% of its revenue from fees charged to recover costs incurred by the Agency to do the vital work it covers.

Given the specialist nature of the MHRA's work, a proportion of our staff are recruited from, or have past employment in, the pharmaceutical industry and/or medical devices industry. First-hand knowledge and experience of these sectors is essential for effective regulation.

In the interests of openness and accountability and to protect staff and the Agency from possible accusations of inappropriate behaviour, the Agency maintains a register of all financial interests in the pharmaceutical and healthcare (medical devices) industries held by staff and members of their immediate family and also of any other relevant interests.

Without exception, all members of Agency staff are required to immediately declare any financial or other interests as and when they arise and make a declaration every year even if a nil response.

In addition to declaring financial interests, members of staff also consider whether there is any other matter which could be regarded as affecting their impartiality, whether this be in relation to pharmaceutical or medical devices work, or the research and scientific work the Agency is involved in.

Staff members can't hold direct financial interests in the pharmaceutical and healthcare (medical devices) industries.

Newly appointed staff will be required to dispose of such interests before taking up employment with the Agency. Exceptionally a transition period of no more than 3 months may be agreed with the Divisional Director. In such cases the interests must be declared on the Conflict Of Interest (COI) register. Similarly, staff may not hold any employment or directorships in the pharmaceutical or healthcare (medical devices) industries, nor carry out consultancy or other private work for those industries.

Information in relation to our decisions is made available unless it cannot for legal or other

respect commercially sensitive information.

INDEPENDENT ADVISORY BODIES

For public interest purposes, ministers need the advice they receive on matters relating to the regulation of medicines and medical devices to be impartial. They also need to be able to seek such advice from a wide range of highly skilled professionals who are well regarded in their respective fields and from a range of appointed lay and patient representatives.

A number of independent advisory committees have been established to provide such an advice. These committees can also establish expert working groups to address specific problems.

All members and experts consulted are requested and obliged to declare any conflicts of interest.

Commission on Human Medicines (CHM)

The Commission on Human Medicines was established in October 2005. Its functions are set out in regulation 10 of the Human Medicines Regulations 2012 (SI 2012/1916).

The functions of the Commission on Human Medicines are:

- to advise the Health Ministers and the Licensing Authority (LA) on matters relating to human medicinal products including giving advice on the safety, quality and efficacy of human medicinal products where either the Commission thinks it appropriate or where it is asked to do so
- to consider those applications that lead to LA action as appropriate (eg where the LA has a statutory duty to refer or chooses to do so)
- to consider representations made (either in writing or at a hearing) by an applicant or by a licence or marketing authorisation holder in certain circumstances
- to promote the collection and investigation of information about adverse reactions to human medicines so advice can be given.

The Commission is similarly involved in respect of medicinal products to which relevant EC legislation applies.

The CHM's activities include:

- giving advice on applications for both national and European marketing authorisations and considers further representation against its provisional advice in respect of national applications, either in writing or in person by the company.
- Commissioners also frequently attend the European Committee on Human Medicinal Products (CHMP) meetings as part of the United Kingdom delegation.
- advising on the need for, and content of, risk management plans for new medicines.
- promoting the collection of reports of suspected adverse drug reactions from health professionals and patients through the 'Yellow Card Scheme'. Data from the Yellow Card Scheme is used for the detection of new safety issues and in the investigation of issues raised from other data sources.
- providing advice on the impact of new safety issues on the balance of risks and benefits of licensed medicines and advises on appropriate risk minimisation measures. These may include adding warnings to product information for health professional and patients, restricting the use of a product or, in exceptional circumstances, suspending use of a product and/or revoking the marketing authorisation. In the event of urgent safety issues, health professionals will be informed via a letter from the Chairman of the Commission. Less urgent issues are communicated via a bulletin entitled 'Drug Safety Update', which is issued in conjunction with the MHRA.
- advising the licensing authority on changes to legal status of marketing authorisations.

Devices Expert Advisory Committee (DEAC)

The DEAC is responsible for providing independent, external expert clinical and scientific advice on a wide range of aspects relating to medical devices to help the MHRA in the execution of its role.

DEAC was formed following an independent review by Professor Terence Stephenson in 2013 on the MHRA's access to clinical advice and engagement with the clinical community. DEAC also supports MHRA in developing and maintaining collaborative relationships with clinical professional bodies.

The role of DEAC is to provide advice to MHRA on the following 'core' areas:

1. Strategic

- Clinical and scientific aspects of medical device safety, usage or introduction with particular reference to areas that represent the highest health risks.

- Device regulatory issues in the context of wider policies across the UK or International healthcare sectors.
- The development of device-related policies with particular reference to 'real world' clinical practice.
- The preparation of papers and position statements illustrating and reflecting the work and achievements of the Devices Division.

2. Communication

- The most effective format, content and distribution channels for targeted medical device-related communications between MHRA and the healthcare community and public.

3. Professional Networking

- Connections and collaborations with professional bodies and their safety committees.
- Emerging issues and 'horizon scanning' for topics that might influence operational activity and MHRA policy.
- Developing and maintaining a register of experts (professional, patient and public).

4. Quality Assurance

- Internal audit support.
- Training support, for example CPD opportunities for staff in the Devices division.
- Oversight of more specialist Expert Advisory Groups.

5. Professional advice

- 'Ad hoc' support for the MHRA devices division in undertaking its operational activity.
- Resolution of matters of dispute.

6. e-Health

- Regulatory issues relating to clinical software and e-Health.

BRIEF OVERVIEW OF HOW WE REGULATE

The regulatory regimes for medicines and medical devices are similar in some ways but are very different in others and as such have their own unique regulatory processes. An online article published in the journal of the Royal College of Physicians (co-written by a former Agency CEO) entitled ‘Regulation of medicines and medical devices: contrasts and similarities’ outlines these different regulatory regimes. It can be read here.

The regulation of medicines and medical devices share similarities on how products are regulated once they are on the market and in use. Broadly speaking, both have similar systems for:

- receiving reports of problems with products;
- issuing warnings if problems are confirmed after investigation;
- inspection of manufacture to ensure that companies comply with regulations and;
- law enforcement, if necessary.

Licences – or market authorisations – for a medicine and CE marking for a medical device are intended to provide assurance that a product’s safety has been assessed before marketing, together with its efficacy (for medicines) or performance (for devices).

The MHRA is concerned about the safety, quality, performance and use of a medicine or device throughout its life.

Medicines

The MHRA grants licences for medicines through various routes to make medicines available. The 'national' procedure involves granting UK only valid licences while those granted via the decentralised procedure (DCP) route ensures companies can market their medicines in the UK and other named EU countries.

The MHRA also grants licences to companies who already have a national licence in one or more EU countries but want to market it in others through the mutual recognition procedure (MRP). Most new types of medicine are now licensed by the European Medicines Agency (EMA) through the Centralised procedure to ensure that they are available to patients and used in the same way across all the member states (MS).

The MHRA will continue to seek and require additional information on risk and benefit, particularly since the initial authorisation or compliance with requirements may have been based on limited information. If the relationship between risk and benefit changes, so may the approval or classification of the product, or the advice to prescribers and users.

Medical Devices

In general, a medical device cannot be marketed in Europe without carrying a CE mark of conformity and this pre and post market assessment is the responsibility of the manufacturer and a notified body (as appropriate). CE marking for a device is a claim of compliance with the relevant safety, quality and performance requirements of the relevant legislation made by the manufacturer, and means that the device, when used as intended, works properly.

The competent authority in EC member states, such as MHRA in the UK, is responsible for:

- carrying out market surveillance
- carrying out compliance and enforcement activities
- designating UK notified bodies (NB)
- monitoring NB performance, which is undertaken by regular audit of their activities. These audits are confidential. MHRA also checks that notified bodies review manufacturers' post market surveillance activities. Notified bodies normally do this as part of their general assessments of manufacturers.

Medical devices can be classified into four risk categories – class I, class IIa, class IIb and class III. For the lowest risk devices (class I devices), such as unmedicated bandages and dressing, manufacturers can self-certify their conformity with the legislation. For all other devices, conformity with the legislation must be assessed by an independent certification body, called a notified body, before the CE mark can be affixed.

Manufacturers can apply to any notified body in the EU and following an appropriate assessment, the notified body will issue relevant certification. This allows manufacturers to put CE marks on their products and put them on the market in the EU. The legislation places obligations on manufacturers to ensure that their devices are safe and fit for their intended purpose before they are CE marked and placed on the market in any EU member state.

Once a medical device has been placed on the UK market, the manufacturer must continue to monitor the product, and report certain adverse incidents to the competent authority, which is MHRA in the UK.

WHEN IS A MEDICINE ACCEPTABLY SAFE?

No product is 100 per cent safe, because all products have side effects. These may be very minor, but they may also be serious.

For example, cancer treatments may make the difference between living and dying. They can also make patients feel very unwell and increase the chances of infections. Aspirin reduces inflammation and fever. But it can also irritate the lining of the stomach.

Different people respond to medicines differently. Several factors can influence the chances of side effects. These include the prescribed dose, the condition being treated, the age and sex of the patient, and other treatments which the patient may be taking, including herbal/ complementary medicines.

Medicines are very thoroughly trialled on thousands of people and must meet rigorous standards before they are licensed. When used more generally by a wider population, other side effects can come to light.

The key questions for the MHRA are:

- Do the advantages outweigh the disadvantages of taking the medicine?
- Does the medicine do the most good for the least harm for most people who will be taking it?
- Are the side effects acceptable?

A high level of side effects may be acceptable for a medicine used to treat a life-threatening illness, for example, but not in one used for a common minor ailment.

Ultimately, patients and their healthcare professionals have to weigh up the pros and cons of each medicine when deciding on the most appropriate treatment.

MONITORING THE SAFETY AND QUALITY OF MEDICINES

There are several ways in which the MHRA checks the safety and quality standards of medicines and ensures that they comply with European and UK law and regulations. Inspections, reporting systems, and intelligence about illegal activity all play key roles.

As well at its own inspection teams and proactive monitoring, the MHRA relies on manufacturers, healthcare professionals, and the public to report defects, side effects, and misleading information.

The MHRA monitors safety and quality standards by:

- Regular inspections of good and safe practice, including:
    - Medicines manufacture and supply
    - Medicines distribution and storage
    - Clinical trials
    - Laboratories testing medicines
    - Inspection of blood establishments.
- Annual routine sampling of marketed medicines at manufacturers' premises, wholesalers, and pharmacies.
- Publishing standards on ingredients and expected quality for medicines (British Pharmacopoeia).
- Ongoing reports from healthcare professionals, patients, and manufacturers, including:

    - Potential side effects of prescription and over the counter medicines and herbal remedies (Yellow Card Scheme)
    - Defective medicines
    - Serious side effects involving blood and blood components (SABRE).
- Reviews of important new evidence on products
- Commissioning research into medicines safety
- Assessment of misleading or incorrect information, including:
    - Adverts
    - Product labelling
    - Product information leaflets.
- Gathering intelligence about illegally manufactured imported and counterfeit medicines and medical devices.
- Managing the Clinical Practice Research Database (CPRD), information from which is used to detect healthcare trends and monitor the safety and risk benefit of market licensed medicines.
- Legally enforcing regulations and statutory obligations, including checking on products that are not licensed as medicines.

When a medicine is suspected or known to be unacceptably safe, the MHRA immediately works with manufacturers, wholesalers and healthcare professionals on the most appropriate and timely action to take.

Sometimes this means a product has to be recalled and taken out of the supply chain. By law, manufacturers must report to the MHRA any important defects in medicines. The action taken is determined by the scale of the threat posed to the public's health. The MHRA is committed to responding promptly and appropriately to concerns.

Reports prompt investigations, which can result in the issue of warnings and alerts. The MHRA also has the power to prosecute when regulations have been breached. The courts can impose fines or prison sentences when the law has been broken. And the Agency can withdraw unlicensed/ illegal products from the market.

Warnings (Alerts) can be issued about defective medicines and side effects associated with medicines and blood and blood products. These are sent out to healthcare professionals and organisations, and publicised widely in print and online, including on the MHRA website on GOV.UK.

While warnings about side effects are issued and changes to the prescribing indications or doses made for licensed medicines, few medicines are withdrawn from use. That is because most work well and are acceptably safe.

WHEN IS A MEDICAL DEVICE ACCEPTABLY SAFE?

No product is 100 per cent safe, because all medical devices may have risks associated with its, no matter how small.

The Medical Devices Directives and the new Medical Device Regulations lays down rules in the essential requirements (available online, see Annex I) relating to the design and manufacture of medical devices so that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient.

The manufacturer must conduct a risk assessment to demonstrate that all hazards have been identified and that the risks have been removed or reduced as far as possible and constitute acceptable risks when weighted against the benefits to a patient. This forms part of a wider systematic risk management process of risk evaluation, control and reduction throughout the entire life-cycle of a device (pre and post production), and is carried out by the manufacturer, requiring regular systematic updating. This process is defined in 'ISO 14971 risk management of medical devices' and compliance with this standard is a key component in demonstrating compliance with the law. Any residual risks must be provided in the instruction for use that are provided with the device.

Even if every conceivable safety measure is performed there will always remain an element of 'risk' associated with the use of medical devices and surgery, however small. The final decision of what is an acceptable risk for any condition and for any individual patient ultimately rests with the clinician and patient, and this is at the heart of the informed consent process, supported by information within the manufacturer's instructions made available to clinicians.

MONITORING THE SAFETY AND PERFORMANCE OF MEDICAL DEVICES

Once the medical device is on the market it is the responsibility of the manufacturer, together with their notified body, to ensure it remains compliant the law, and works as intended. If there is a safety or performance problem, MHRA will become involved to protect public health.

Manufacturers are required to point out benefits and any risks associated with the device in the instructions for use. However, the final decision to use a medical should be made between the patient and healthcare professional, after discussing all the options and recognising the benefits and risks in the context of the condition being treated, subject to NHS and NICE guidance and is at the heart of the consent process.

Manufacturers are legally obliged to report certain adverse incidents involving their products when there has been, or there is the potential to cause, a death or serious injury. Healthcare professionals and their patients or carers can report problems about devices to the MHRA's Yellow Card adverse incident reporting scheme. For example, users might find that the labelling and instructions for use of a medical device are unclear, leading to improper use. Adverse incidents can also arise from patients and healthcare professionals through use error, intended or otherwise.

These reports help manufacturers improve their design and product information, and they also help MHRA improve the safety of devices.

A key MHRA responsibility is to investigate device-related adverse incidents or monitor investigations carried out by the manufacturer, and take appropriate action to prevent or reduce the likelihood of recurrence as part of its market surveillance role. This also includes enforcement and a statutory obligation to resolve any non-compliances with the requirements of the legislation that are found during the investigation. It has a risk-based enforcement programme in line with the Hampton Report which assesses all allegations of non-compliance that come to its attention and will take whatever regulatory action is felt to be appropriate.

Further information is obtained before we determine our response, which may be:

- a Medical Device Alert, giving advice to the healthcare service, and/or
- a requirement for the manufacturer to make appropriate changes in design or
- information, or
- a product recall, or

- sending the data to the manufacturer and storing it in MHRA's database to help us spot trends that require action.

These safety monitoring systems in place helps us to identify adverse incidents and take prompt action. The majority of non-compliances with the legislative requirements are resolved through voluntary cooperation with the manufacturer but MHRA has a series of powers and sanctions available to it under the Consumer Rights Act 2015 and the Consumer Protection Act 1987, including the removal of a product from the market and prosecution that it can use to take formal enforcement action where necessary.

Furthermore, MHRA works with other European countries to ensure that only compliant devices are placed on the market.

Sometimes the instructions for use or labelling are unclear. Sometimes, patients and healthcare practitioners simply do not use a device or piece of equipment in the way in which the manufacturers intended.

Ultimately, patients and their healthcare professionals have to weigh up the pros and cons of each medical device when deciding on the most appropriate treatment.

WHO MAKES THE DECISIONS ABOUT THE SAFETY AND PERFORMANCE OF MEDICINES AND MEDICAL DEVICES?

There are three main groups within the MHRA involved in regulatory decisions:

- Staff – the Agency's professional staff make many decisions about the safety and performance of medicines and medical devices on a day-to-day basis, and about the
- quality of manufacturing and the distribution of medicines. An Executive Board of senior staff oversees the work of the Agency and takes ultimate responsibility for the decisions made.
- Advisory Committees – groups of independent experts and lay representatives who advise on whether medicines and devices work and are acceptably safe, based on an evaluation of all relevant evidence, including that from the MHRA. These groups include the Commission on Human Medicines, its Expert Advisory Groups, and the Devices Expert Advisory Committee.
- The Agency Board – which is made up largely of external members, acts in a supervisory and advisory capacity and has a particular role in assuring the quality of decision-making.

In law, decisions by the Agency are decisions of the Secretary of State for Health who is accountable to Parliament. Ministers also make decisions on matters of significant public concern from time to time, advised by the Agency or its expert committees.

There are other organisations and bodies outside MHRA which are also concerned with safety, quality and/or performance, principally in that:

- Independent third-party organisations called notified bodies carry out a compliance assessment before manufacturers can place certain medical devices on the market. Notified bodies in the UK are designated and audited by MHRA.
- Many decisions made by or within other Member States of the European Union and by the European Medicines Agency must be respected or taken into account within the UK, just as decisions of MHRA can have an impact on other Member States. Experiences of problems are also shared in both directions.
- Clinical trials of products are subject to the approval of ethics committees, complementing the role of MHRA, which is principally concerned with the scientific evidence.

We do not and should not have direct influence over ethics committees or European partners but recognise that their decision-making often follows similar principles; if we have cause for concern about decisions taken by others, we make that known through appropriate channels.

It is for doctors and other healthcare professionals to determine the suitability of particular

medicines or medical devices for individual patients under their care, weighing benefits against risks and subject to guidance from the NHS and NICE.

Patients and the public will often have their own views about the suitability of particular medicines or medical devices. They are usually free to decide for themselves whether to use the products or not, supported by reliable information about risks and benefits.

We encourage both patients and healthcare professionals to report adverse events, through the Yellow Card Scheme for medicines and devices. These reports are important to the MHRA, which analyses them alongside other new sources of information to determine whether action is needed.

HOW WE ENGAGE WITH PATIENTS

We recognise and value the contribution engagement makes to informing the work of the Agency. The Agency takes advice from leaders in their field and this informs and shapes our thinking. We also recognise that for our safety information and regulatory action to be successfully embedded in healthcare practice it is essential to successfully engage with health system leaders and front-line health and social care professionals as well as patients and the public. We recognise that patients and the public have unique knowledge and experience we can draw on to support our work.

Much of our engagement is in conjunction with or through third parties who have effective channels to patients and represent patients' interests. We have learnt from others in developing our key patient and public engagement mechanisms, noting that what works for one organisation may not be the right approach for another, and we work collaboratively with these and other bodies as necessary.

We have established a cross-agency workstream to bring together patient and public engagement interests, ensuring a co-ordinated and cohesive approach. It is important to recognise that patients and the public are not a homogenous group and therefore our approach is targeted rather than 'one size fits all', with an emphasis on using established channels rather than always developing additional ones.

We have also established a corresponding workstream on healthcare professionals to ensure that we are able to adequately engage with the front-line to ensure our regulatory action, that safety information is implemented in a timely manner and that healthcare professionals are able to raise any concerns and potential barriers with us. We also recognise that healthcare professionals are an important conduit to patients.

The Commission on Human Medicines has in the past convened an Expert Advisory Group on Patient and Public Engagement with a remit to consider optimised communications on medicines to both healthcare professionals and patients, and to consider patient involvement in the medicines licensing process. The group will shortly be reconvened to consider and advise on the communication of drug safety messages in the digital age.

A key channel of engagement with patients and the public is via the Agency's Patient Group Consultative Forum (PGCF), which has over 100 participants who are either representatives of patient groups/networks and research charities or individual patients in their own right. The PGCF brings the patient voice into the Agency, where hearing the views and perspectives of patients can assist in developing matters of policy or the approach to a particular regulatory area. Such a mechanism is important in informing our thinking and

decision making to ensure we learn from the experiences of patients and that project outcomes maximise public health.

The PGCF also assists in the recruitment of individual patients to participate as experts, in relation to their lived experience of a particular health condition or use of a specific medicine, in ad hoc advisory groups of the CHM. In developing our Valproate Stakeholders' Network (VSN) we ensured that we included representatives from the relevant health charities but also, importantly, the campaign groups that represent the families affected. The patient and campaign group input to the VSN has been instrumental in helping develop the UK-specific materials for communicating the strengthened regulatory measures to both healthcare professionals and patients. The VSN has also helped to raise awareness of the new measures through the participating groups' own communication channels, including social media and wider supporter networks.

THE CENTRAL ALERTING SYSTEM (CAS)

Background

- CAS is used to issue alerts to the NHS and independent and social care providers.
- Issuing a CAS alert involves publishing the alert to the CAS website, whilst generating an email to mailing lists of subscribers whom the alert originator has deemed the alert relevant to.
- The email includes a direct link to the alert (which will open a pdf) and provides a very high-level summary of what the alert covers.

Publication of alerts/messages

- Most alerts/messages can be viewed on the CAS website.
- Alerts/messages can be 'hidden' from the public view of the CAS website, meaning a visitor to the site who does not have login information will not see the alert. This option is exercised if an alert contains information which could help a patient harm themselves, or if there is a contractual reason not to publish information, which is the case with high and low voltage facilities notices which are received from the Energy Networks Association.
- For some bodies/teams issuing alerts/messages, CAS may be the only place the alerts/messages are published, but most maintain their own website areas in addition to CAS.

'Action' (response) and 'Information' (no response) recipients

- The system is designed to recognise 'Action recipients' and 'Information recipients', the 'action' in this context is whether the recipient will be required to log into the website to confirm actions taken. Whether an alert will require action from the receiving organisation is a judgement call for the organisation to take based on the content of the alert and the services they provide.

Trusts responding on CAS ('Action recipients')

- NHS Trusts (including acute, specialist, mental health, LD, community and ambulance trusts) receive an email notification when an alert has been issued and are required to log into the website and a) acknowledge receipt (which must be within two working days) and b) to record 'action completed', or 'action not required'.
- There will be a completion deadline set for part b) which is decided by the alert originator based on the urgency of the alert and/or the nature of the actions they are asking organisations to undertake.

- At such organisations a CAS Liaison Officer is in place, who provides the main interface with the system, receiving alerts and initiating whatever processes are in place within their organisation to react to alerts. CAS Liaison officers in trusts typically work within a facilities team, risk management team, governance team or medical device related role.
- Because of the complexity of services that NHS trusts provide, CAS does not selectively target alerts/messages to different types of NHS Trust, but sends them to all types of NHS trust.
- An alert will remain 'open' against an organisation (or regional team) unless the organisation sets the status of the alert to 'Completed' or 'Action not required' via the CAS website.

Regional cascade from CAS

- Regional Offices of NHS England receive email notification of alerts/messages issued as above.
- If the issuer of the Alert/message requires cascade to general practice providers, NHS dental practices and/or community pharmacy, then this will be made clear in the alert email received from CAS. Such action should be undertaken within two working days, usually via a locally maintained email list (some offices cascade via others (e.g. to sub-regional teams or CSUs).
- Whilst the regional office will record 'Completed' or 'Action not required' via the CAS website at the point they have completed the onward cascade, responses are not collected from the general practices or community pharmacies.

Organisations and individuals not responding on CAS ('Information recipients')

- CAS also sends alerts to a range of other recipients, mainly non-NHS care providers, but does not collect responses from them. The bulk of these recipients exist on two lists: 'Independent healthcare providers' and 'Social Care providers', with the latter list, containing care homes, considerably the larger of the two. It is up to the alert originator as to which lists they choose to send their alert to.
- When such providers register with the system they are advised that alerts will be sent to them for information and action where appropriate (e.g. NHS Improvement Patient Safety Alerts apply to all providers of NHS-funded care). Segmented lists of different providers e.g. listings of independent hospitals, independent dental practices etc, are not held; as such targeting is very limited, placing the onus on organisations to check the relevance of the alerts they do receive.
- These subscriber lists come, in the main, from voluntary subscriptions whereby organisations have registered with the system over time since its inception. These have been supplemented in the past, by taking data from the CQC of organisations that have registered with them over a certain time period, with those organisations then contacted directly and invited to register. However, there is no systematic process to ensure all such providers are registered.
- There are no set exclusions to who can and cannot register to receive alerts. Those who receive login access have historically been restricted to NHS organisations, as they can access compliance data (see section below). Similarly, there are contractual reasons why high and low voltage notices are not published, so caution would be taken before registering any individual from an organisation that could be using CAS as a means to receive these alerts as a healthcare organisation would.

Types of alert/message where responses are not collected from any provider

- CAS does not collect responses to MHRA Drug Alerts, alerts/messages from the Chief Medical Officer (CMO) or MHRA Dear Doctor Letters from any provider, including trusts and Regional Offices
- These issues which such alerts can cover, and the speed at which they may need to be communicated, means that these alerts can be issued 24/7.
- Whilst issuing out of hours is a rare occurrence it is still critical system functionality (note the Cyrus Project alert from the CMO issued out of hours on 02 August 2018).
- As these alerts can be issued out of hours they are targeted to slightly different mailing lists (for example medical directors and chief executives) to try and ensure as far as possible, that there will be individuals available to pick them up. Note that at present these lists are used for alerts issued in and out of office hours.

Self-declared CAS compliance data

- For those types of alerts/messages that require a response, and those types of organisations required to provide a response (mainly NHS trusts) compliance data on whether they have self-declared action complete within deadline is compiled within the system.
- This data is used by NHS Improvement, NHS England, the Care Quality Commission and the NHS website (formerly NHS Choices). The CQC uses all Alerts requiring a response to derive its metric but does not publish this data; the published versions are based on NHS Improvement Patient Safety Alerts

CAS development

- CAS itself has recently transferred to the Medicines and Healthcare products Regulatory Agency (Agency). The day to day operation has rested with the MHRA since 2012, but the IT platform has remained the DH platform developed and introduced in 2008. The IT has now been re-platformed, with end of life components replaced, with a lift and shift approach followed.
- Further development of the system is something the MHRA is open to. Where this requires further investment then further discussion with partners to understand how this will be met will be held.

Annex B: Detailed Points and a Timeline for Q1 on HPTs

1a) Timeline

A detailed chronology of events from 1950, when the first Hormone Pregnancy Test was marketed in the UK, to October 2014 (when the then Minister for Life Sciences requested an independent review of the issue) is summarised in Annex 3 to the report on the CHM website. This was based on information received from a number of sources and represents the perspective of the regulators (MHRA and its predecessors), marketing authorisation holders, academic researchers, government, legal profession and the media.

A simplified chronology of events from 1950 to the present day is provided after this section. This includes milestones considered to be of relevance/importance such as: key study publications; actions taken by regulators and companies, primarily in the UK but also other countries; important developments in pregnancy testing; major legislative changes; and the introduction of regulatory guidance.

Main events are also highlighted in the report of the CHM EWG.

1b) Initial recognition and understanding of risk and dates of consequential and significant research studies

A great many studies, letters and reviews have been written on the use of HPTs since they were first introduced to the market. This response gives only a high-level overview of how events unfolded and highlights only the historical studies (when HPTs were still available in the UK) that led directly to action; it does not present a complete record of all publications that were available at that time. Detailed reviews of all the data considered by the EWG are referenced in Annexes 18 – 30 of the EWG report .

In general, publications in the 1960s tended to discuss the outcomes of pregnancies where mothers had been exposed to some of the components of HPTs, including the incidence of spontaneous pregnancy loss and possible virilisation of the female infant, and evaluation of the use of progestogens for the maintenance of pregnancy.

In **1958** Edwards first suggested that the mechanism of action of HPTs could cause congenital anomalies. In October **1967**, the first observational study to suggest a link between use of HPTs in pregnancy and congenital anomalies in the child exposed in utero was published in a letter to the journal Nature (Gal et al, 1967). This study found an increased risk of spina bifida in the babies of mothers who had taken HPTs to diagnose pregnancy. It was published against a background of heightened awareness of the possible teratogenic effect of medicines taken in pregnancy through recent experience with thalidomide and, primarily, phocomelia in the offspring. The Committee on Safety of Drugs (CSD) sought advice from the Sub-Committee on Adverse Reactions (SCAR) on a letter from Dr Gal's team.

The CSD and its successor the Committee on Safety of Medicines (CSM) took the following steps to further evaluate this potential signal:

- discussion of the study findings with the authors;
- request for manufacturers of HPTs to provide all relevant laboratory data;
- request for relevant information from academics working in the field;
- exploration of possible collaboration on studies with those working with congenital anomaly databases;

- initiation of a long-term questionnaire study (the CSM Maternal Drug Histories study): “Maternal drug histories in babies with congenital abnormality”, to examine a possible association between HPTs and cleft palate/hare lip, spina bifida and hydrocephalus and reduction deformities of limbs;
- regular consultation with the CSD and CSM expert committees as new data emerged.

Gal’s study in 1967 stimulated major research interest in the issue and many further epidemiological studies were published thereafter until HPTs were removed from the market in 1978. These not only investigated the possible association between HPTs and spina bifida but a range of other congenital anomalies, with conflicting findings.

During the HPT EWG review in 2015-2017, a critical consideration was that, being carried out in the 1950s to 1970s, the design, conduct and quality of the studies were largely poorer than would be expected of those conducted today. This most likely reflects the lack of available databases and adequate routine data collection at that time coupled with subsequent advances in knowledge and understanding of study design and analysis. Furthermore, when HPTs were first marketed, pharmaceutical companies were not legally required to ensure that the medicines they marketed met appropriate standards of safety, quality and efficacy. This had an important impact on the type of data available for the review, the quality of those data, and the interpretation of the study findings.

A very careful evaluation of the available data was therefore necessary to determine whether it supported an association between congenital anomalies in the children of mothers who had been given an HPT during early pregnancy as being causal, or whether its limitations were such that the association was more likely to have been due to chance or to other factors. All studies were assessed according to a pre-defined set of quality criteria, to indicate for each whether the quality was considered to be good, moderate or poor quality, respectively. An overall quality score for each study was not produced as the criteria were not considered to be of equal importance; and the EWG felt that to develop a weighting system for the criteria would introduce subjectivity into the system.

Detailed reviews of all the data considered by the EWG are referenced in Annexes 18 – 30 of the EWG report.

1c) Communication of regulatory and professional guidance to clinicians and patients

Based on evaluation of the data that were accruing, scientific uncertainty over the strength of the evidence, and the introduction of the modern in vitro urine-based pregnancy tests, the following precautionary actions were taken between 1967 (when the Gal study was published) and 1978 (when Schering withdrew Primodos from the UK market).

1. In 1969 Schering stopped promoting Primodos for pregnancy testing and ceased providing free samples to healthcare professionals
2. In 1970 Schering removed the indication ‘diagnosis of pregnancy’ from the Primodos datasheet following a recommendation by the UK Standing Joint Committee on the Classification of Proprietary Preparations (otherwise known as the MacGregor Committee) that pregnancy tests should no longer be reimbursed by the health service
3. In 1975, when the interim results of the CSM study became available (Greenberg, 1975):
    a. CSM sent a letter to all UK prescribers advising them not to use hormone tests for diagnosing pregnancy because of the possible hazard and the availability of other means of diagnosing pregnancy (Annex 15 of the EWG report)

b. CSM published an early warning letter in the BMJ (Greenberg et al 1975)

c. Schering updated the Primodos datasheet and package insert to include i) a warning about the possible risk of congenital anomaly and ii) a contraindication in pregnancy

d. Schering sent letter to all GPs, gynaecologists and family planning doctors

e. Schering asked 'Chemist and Druggist', 'Retail Chemist' and 'The Pharmaceutical Journal' to publish a statement about a possible risk of fetal anomalies and advise the printing of adhesive labels to be added to packaging warning that HPTs should not be used in pregnancy

4. In 1977, reports that Primodos was still being used as a pregnancy test prompted CSM to issue a reminder to all UK doctors and pharmacists that these products should not be used for this purpose (Annex 17 of the EWG report). The timing of the reminder coincided with publication of the final results of CSM's 'Maternal drug histories' study (Greenberg, 1977).

5. In 1978 Primodos was withdrawn from the UK market by Schering, reported to be for commercial reasons.

1d) Events leading up to the EWG review on HPTs

In the 1970s, the 'Association for Children Damaged by Hormone Pregnancy Tests' ('The Association') brought legal proceedings against the manufacturer of Primodos, Schering (now Bayer). In 1982 the case was discontinued by the Association with the judge stating that "the evidence would have to be very strong for a new trial".

In May 2009, a former Chair of the Association for Children Damaged by HPTs contacted MHRA and after extensive correspondence met with the Agency in December 2010 and with the Department of Health and Lord Alton's researcher in January 2011. At the December 2010 meeting MHRA offered to review any relevant scientific evidence they thought should be considered and repeated this offer again in November 2011 and December 2012.

In February 2012, an Early Day Motion calling for a public inquiry was tabled by Yasmin Qureshi MP and in July 2012 MHRA met with Esther McVey MP, then Minister for Disabled People. In January 2014 MHRA met with Yasmin Qureshi MP and Dan Poulter MP, then Parliamentary Under Secretary of State for Health, who asked MHRA to provide a summary of findings from the historical evidence. We subsequently published this summary on the MHRA website.

A body of information accrued by the Association and other patient groups largely from the National Archives, and continued pressure from the All-Party Parliamentary Group on HPTs and campaigners culminated in a debate on HPTs in the House of Commons by the Backbench Business Committee on 23 October 2014. During the debate a number of speakers referred to the need to consider whether a causal link between HPTs and birth defects could be confirmed. George Freeman MP, the then Minister for Life Sciences, stated that he would instruct that all relevant documents held by the Department of Health be released and that an independent review of the papers and available evidence be conducted.

In 2015 the Commission on Human Medicines (CHM) established an Expert Working Group to review the available data on a possible association between HPTs and adverse outcomes in pregnancy, and to make recommendations to the Licensing Authority (Health Ministers).

To ensure the review was comprehensive, the MHRA gathered published and unpublished evidence from a number of different sources including: pharmaceutical companies whose predecessors used to market HPTs; medicines regulators in other countries; the UK National

Archives; archives in Berlin (the Landesarchiv Berlin); anyone who considered they had any relevant information following a public call for information; and from the published literature. The EWG also heard evidence from several scientific experts, and members of The Association were invited to relate their experiences to the EWG.

When considering the evidence for a possible association between use of Primodos to diagnose pregnancy and having a baby with a congenital anomaly, the EWG set out the key conditions that in the Groups' view would need to be met for this to have been possible (Chapter 4):

1. Primodos must be administered during the critical period of fetal development
2. It must be able to cross the placental barrier between the mother and the fetus
3. The fetus must have estrogen and progesterone receptors that are capable of binding to the hormonal components of Primodos
4. These receptors must be present during the critical period of fetal development and be able to bind to, and be activated by, the drug
5. The drug should be at a sufficiently high concentration to cause a biological effect.

To assess the five points above, the EWG examined a wide range of data to determine whether the available evidence supported a causal association between HPTs and miscarriage or congenital anomalies. Types of data included:

1. Studies in animals to determine whether norethisterone or ethinylestradiol, or both, can act as a teratogen and cause malformation or a miscarriage (Chapters 5.1 and 6.2 of the EWG report);
2. Evidence for an indirect effect on the pregnancy caused by disruption or interruption of the intrauterine blood supply as a possible mechanism for congenital anomalies (Chapter 5.1 of the EWG report);
3. Personal experiences from 13 members of the 'Association for Children Damaged by Hormone Pregnancy Tests' who had, or whose child had had, one of a range of different anomalies (Chapter 5.2 of the EWG report);
4. Reports of suspected adverse drug reactions (ADRs) received from a number of sources, including the Yellow Card Scheme (Chapter 5.2 of the EWG report); and
5. Epidemiological studies on a possible association between the use of norethisterone or ethinylestradiol, or both, to diagnose pregnancy, to maintain pregnancy or to prevent pregnancy, and risk of miscarriage or the development of congenital anomalies in the child (Chapters 5.3 and 6.3 of the EWG report).

The Group also considered what developments have taken place since HPTs were on the market in terms of identifying, evaluating, managing and communicating safety concerns with medicines in pregnancy and what opportunities existed for further strengthening the systems in place (Chapter 7 of the EWG report).

1e) Newly published evidence relevant to HPTs

In October 2016 a researcher from Aberdeen University (Professor Neil Vargesson) presented preliminary work on chicken and zebrafish embryos to the EWG which found dose-dependent damage in zebrafish embryos (small eyes and ears; bent spines; yolk sac damage; loss of movement) but no developmental effects of norethisterone acetate and ethinylestradiol on chick embryos, even at very high doses. Although these were pre-publication data and therefore not retained by the Group, the EWG included reference to these studies as part of the non-clinical scientific evidence reviewed by the EWG (as described on page 39 of the final report of the EWG). When the report of the EWG was

published in November 2017, the research on zebra fish embryos had not been accepted for publication.

Once the zebrafish work had been published (Brown et al., 2018), Ministers asked the CHM to conduct a review by setting up a new group of toxicology experts to advise the CHM on: the suitability of the zebrafish model for evaluating effects of norethisterone and ethinylestradiol in human pregnancy; the robustness of the study; and any clinical implications. The meeting of the Expert Group took place on 5th October 2018 and on 11th October the CHM concluded that while well-conducted, there are no implications from the publication of Brown et al. for the clinical use of medicines currently on the market. Final minutes of the Expert Group are available.

MHRA also asked the European Medicines Agency's Committee for Medicinal Products (CHMP) to issue an opinion on the implications of the Brown et al publication for currently authorised products containing norethisterone acetate and ethinylestradiol, the components of Primodos, under Article 5(3) of Regulation (EC) No. 726/2004. The terms of reference of the EU and UK reviews were aligned but the EU review was completely independent of the CHM process with no active participation by the UK. The publication of Brown et al. was considered by the CHMP at its meeting in October and its findings are consistent with those of the CHM review.

Conclusion

Evidence on a possible association between HPTs and adverse pregnancy outcomes has been reviewed on a number of occasions in the UK: by the CSM when HPTs were available in the UK; by the MHRA in 2014 in response to a request by Dan Poulter MP, then Parliamentary Under Secretary of State for Health; and by a CHM EWG in 2015-2017 in response to an instruction by George Freeman MP, then Minister for Life Sciences. Most recently the Brown et al data in zebrafish embryos has been reviewed by a CHM Expert Group of toxicologists and by the EU CHMP.

All reviews have been consistent in finding that the available evidence does not support a causal association between HPTs and adverse outcomes of pregnancy.

A simple timeline of events for HPTs

Note: This simplified timeline includes milestones considered to be of relevance/importance and includes: actions taken by regulators and companies, primarily in the UK but also other countries; key study publications; important developments in pregnancy testing; major legislative changes and introduction of key guidance.

Noteworthy actions taken with Primodos in the UK are emboldened.

Abbreviations:

CHMP – Committee for Medicinal Products for Human Use

CSD – Committee on Safety of Drugs

CSM – Committee on Safety of Medicines

CHM – Commission on Human Medicines

DH – Department of Health

LO'S – Lord O'Shaughnessy

RCGP – Royal College of General Practitioners

SCAR – Sub-Committee on Adverse Reactions

SCL – Schering Chemicals Ltd (UK)

SWP – Safety Working Party

Date	Event
1950	Amenorone and Orasecron becomes available in the UK Duogynon becomes available in Germany
1951	Menstrogen becomes available in the UK
1952	Disecron available in the UK by this time

1958	Oral Duogynon introduced in Germany Thalidomide becomes available in the UK
July 1958	Primodos oral becomes available in the UK - 10mg NET and 50µg EE, 1 daily for 4 days
July 1958	First reference to possibility that mechanism of action of HPTs could cause potentially fetal malformations (Edwards, Br J Prev Soc Med)
Mar 1960	Primodos oral reformulated – 5mg NET and 10µg EE, 1 daily for 2 days
1961	Secrodyl becomes available in the UK Dose of Duogynon doubled to induce more rapid withdrawal bleed Thalidomide withdrawn in the UK
1962	Duogynon Forte introduced in Germany
Oct 1962	Jacobson describes reports of virilisation with the use of norethisterone for the maintenance of pregnancy
1963	Primodos oral reformulated – 10mg NET and 20µg EE, 1 daily for 2 days
June 1963	Committee on Safety of Drugs (CSD) established
1964	Yellow Card Scheme set up
March 1964	First commercial agglutination test for pregnancy diagnosis developed in UK (Gravindex) - has yet to replace toad test in common use; only for diagnosis in cases where knowledge of pregnancy status medically required
May/July 1964	First record of consideration by Sub-Committee on Adverse Reactions (SCAR) of adverse effects with HPTs – 2 cases of abortion with Primodos, and 1 congenital anomaly each with Amenerone and Primodos, out of a total 738 ADRs reported to the CSD's Register of Adverse Reactions
Nov 1964	Dr Inman investigates whether retrospective survey of births in Edinburgh may help obtain further information about congenital abnormalities associated with use of drugs
1965	Norone becomes available in the UK
May 1967	Gal publishes on spina bifida and HPTs in Nature. CSD considers Gal publication, feedback its perceived limitations to the authors and propose meeting.

	Much correspondence between Dr Inman and various experts exchanging views on the findings and requesting further evidence that might shed light on the issue
Aug 1967	UK Ministry of Health circular informs local hospital authorities that Pregnosticon and Prepuerin pregnancy tests had been made 'available to hospital pathology departments on central supply'
Nov 1967	Correspondence between Mr Cooke (independent statistician) and Dr Briggs (Schering UK) on correlation between increase in sales of HPTs and anomalies in the UK
1968-1969	Agglutination pregnancy test becomes favoured over the toad test in NHS
Jan – May 1968	Continuing correspondence between Dr Inman and other researchers, including RCGP, on possible further analyses/studies, including a prospective matched cohort study.
June 1968	Schering UK informs parent company that the question of the safety of Primodos has to be resolved, they are not satisfied that sufficient has been done to remove suspicion cast on Primodos and that the onus of proof of safety must lie with the manufacturer. Schering UK proposes joint study with RCGP.
1969	CSD advises companies to stop promoting HPTs **Schering stops promoting Primodos as a hormone pregnancy test and withdraws samples from sales representatives** Internal Schering documents state "only two tests had been carried out with Primodos and those had been in 1969... certain aspects of the results of these tests, should have been investigated further…" Ongoing correspondence between Dr Inman and various researchers about the possibilities of gathering additional human data. Ongoing correspondence with RCGP researchers over findings of RCGP studies in England, Wales and Scotland CSD initiates study on Maternal Drug Histories in collaboration with Registrar General. Letter sent from CSD to all physicians requesting their assistance. Correspondence between Schering and Dr Gal over conducting future joint animal tests.
Jan 1969	Norone discontinued in the UK
Feb 1969	Schering AG sends letter to Schering UK advising no need to withdraw Primodos oral

	Letter Dr Inman to Schering UK states the information they have provided is unhelpful in making a decision about Primodos Dr Inman tells Schering UK much more work needs to be done and recommends Schering conducts tests in dogs and primates (in addition to rats).
Mar 1969	Disecron discontinued in the UK
July 1969	Schering UK proposes to Schering AG that further studies with primates necessary
Aug 1969	Dr Inman requests data from teratogenicity studies on all Schering hormone preparations and estimate of number of samples distributed
1970	CSD becomes Committee on Safety of Medicines (CSM) Norwegian regulator removes indication diagnosis of pregnancy for HPTs. Primodos remains on the Norwegian market as 20 tablet pack for secondary amenorrhoea. Schering internal documents refer to clinical trials of: combination of active substances based on norethisterone (SH 376), 1956 - 1957, about 1 year Duogynon dragées with 5 mg norethisterone acetate 1947 - 1958, about 1 ½ years Duogynon dragées with 10 mg norethisterone acetate 1961 - 1962, about 1 year
Feb 1970	Primodos oral indication in diagnosis of pregnancy removed from company's datasheet on recommendation of UK Standing Joint Committee on the Classification of Proprietary Preparations (MacGregor Committee); ABPI datasheet updated; indication retained in all non-UK Schering products.
July 1970	Schering UK agrees to delete pregnancy testing as indication for Primodos and update UK package insert text – request confirmed and actioned by Schering AG
Nov 1970	In Sweden deletion of indication 'early pregnancy diagnosis' for Duogynon Forte, Duogynon Injection and Primodos Forte requested by Swedish agency; does not appear to have been implemented immediately by Schering
Pre-1971	Paralut discontinued in the UK
1971	Medicines Act comes into force First home pregnancy test 'Predictor' launched in UK

	In Italy pregnancy test removed as indication for Duogynon Primodos oral withdrawn at renewal in Finland due to concerns about appropriateness of the regulatory process (not abnormalities). Primodos simplex injection remains on Finnish market until 1978.
1972	CSM enlarges study on Maternal Drug Histories Indication 'pregnancy diagnosis' deleted for Primodos Forte
Feb 1972	Schering applies for a product licence of right (PLR) for Primodos for the indication of 'secondary amenorrhoea' Roussel apply for a PLR for Amenorone (for indications related to disorders of menstruation and amenorrhoea), and for Amenorone Forte (foe indications in secondary amenorrhoea and as a pregnancy test)
Nov 1972	Gal et al provide further details of their findings from the study published in 1967 in Nature
Nov 1972	**PLR granted for Primodos for 'secondary amenorrhoea'**
1973	In Sweden indication of pregnancy test removed from Duogynon Forte and Duogynon injection
April 1973	PLR granted for Amenorone (for disorders of menstruation and amenorrhoea), and for Amenorone Forte (for secondary amenorrhoea and as a pregnancy test)
May 1973	SCAR recommends extending their study to obtain results from larger numbers on the basis of "some potentially quite striking findings".
Oct 1973	Notice from FDA: the potential risk of teratogenic effects is considered high enough to warrant removal of pregnancy related indications from the labelling of progestogens
Dec 1973	Licence for Amenorone Forte varied to remove 'pregnancy test' as an indication
1974	In Spain the indication diagnosis of pregnancy was removed for Primodos at the request of the company
Jan 1974	Letter from Schering AG to Schering UK giving reasons (FDA action) for deletion of 'pregnancy test' from the indications for Primodos in Germany
April 1974	Primodos withdrawn in Norway at the request of the regulator
Nov 1974	CSM consider the interim findings of the Maternal Histories study, note their importance and advise not approaching the companies but finishing and publishing the study as soon as possible.
1975	Norlutin A discontinued in the UK

Jan 1975	SCAR disagrees with CSM re the decision not to approach companies and give an early warning based on the findings of the Maternal Histories study. Schering UK informs Schering AG that Dr. Inman has advised that "over the last five years, drug monitoring in pregnant women had shown, that those who had taken a hormonal test were at a relative risk of 5:1 to have malformed child. The investigation has not yet been completed, but it is to be expected that a corresponding publication will be published within the next six months. In order to avoid unnecessary attention, the unofficial way had been chosen and the concerned manufacturers had already been informed so that they could already take action to prevent medicolegal problems". Dr Inman suggests immediate addition of pregnancy as a contraindication and circulation of updated datacards to all doctors. Schering agrees to a contraindication in pregnancy for Primodos HPTs (Duogynon) withdrawn in Australia on recommendation of Federal Drug Evaluation Committee
Jan-Mar 1975	FDA bulletin issues warning on use of HPTs and possible congenital anomalies
Feb 1975	Withdrawal of Gestest (ethinylestradiol and norethisterone) in the US Secrodyl discontinued in UK **CSM advises that doctors should be warned of the possible risk of anomalies through publication of a letter in the BMJ** In Sweden Primodos Forte taken off market; pregnancy diagnosis as indication permitted again for Duogynon dragee and ampoule.
Mar 1975	Menstrogen discontinued in the UK SCAR approves letter for BMJ and informs manufacturers of study findings
Apr 1975	**Interim results of CSM study on Maternal Drug Histories published in BMJ** Ireland issues warning about HPTs
May 1975	Orasecron discontinued in UK
June 1975	**CSM issues warning about HPTs in 'Adverse Reactions'**- a possible hazard is suggested and doctors should not normally prescribe certain hormonal preparations for pregnancy test.

	CSM advises DH that 'diagnosis of pregnancy' should not be included in licences for such products and that warnings about possible hazard in pregnancy should be included in promotional literature. Schering sends letter to all UK GPs, gynaecologists and family planning doctors about the possible risk and the new contraindication in pregnancy and publishes articles in 'Chemist and Druggist', 'Retail Chemist' and 'Pharmaceutical Journal' Orasecron discontinued in the UK WHO warning on use of sex hormones in pregnancy Gal publishes letter in BMJ suggesting the need for further risk minimisation measures because of continuing use of HPTs
June 1975	Licence for Amenorone and Amenorone Forte varied to introduce a contraindication in pregnancy for both products, and to strengthen the indication for Amenorone Forte to 'secondary amenorrhoea *when pregnancy has been excluded*'
July 1975	**Schering applies to vary the licence for Primodos to add a warning about a possible association between Primodos and congenital anomalies and to contraindicate use in pregnancy**
Aug 1975	Letter from Dr Gal to Chair of CSM highlighting the 8 years use of an unnecessary diagnostic test tablet (since publication of her study in 1967)
Sep 1975	Licence for Primodos varied to introduce a contraindication in pregnancy and warning of a possible association with congenital anomalies
Oct 1975	Note from Dr Inman to Deputy Chief Medical Officer states that CSM is "defenceless in the matter of the 8 year delay"; letter from Dr Inman to Dr Gal suggests the delay was because there was "no more rapid way of assessing the problem".
1976	Mrs Valerie Williams starts Primodos campaign in UK In France Duogynon oral renamed to Primodos
Nov 1976	Dr Greenberg (DH) proposes submitting results of Maternal Drug Histories study to BMJ – these confirm the earlier findings for an association Political interest stimulated in the UK
Dec 1976	Duogynon no longer on sale in Australia

1977	Automatic renewal of licence for Duogynon simplex oily in Germany Duogynon discontinued in Netherlands In Sweden Duogynon oral discontinued. Pregnancy diagnosis as indication removed for Duogynon parenteral.
May/Jun 1977	Amenerone and Amenerone Forte discontinued in the UK
Oct 1977	**Final results from CSM Maternal Drug Histories study published in BMJ** Schering Chemicals sends Dear Doctor Letter in UK
Oct/Nov 1977	WHO issue warning on HPTs
Nov 1977	CSM issue 'Adverse Reactions' leaflet highlighting the results of their study and reminding all doctors in the UK that HPTs should not be used
Nov 1977	Jack Ashley MP asked Roland Moyle (Minister of Health) the first of many questions regarding Primodos namely when the Department first knew about a link, when the link was supported by CSM and what action the Department took; he also raised the issue of whether Primodos would be banned, of compensation, and whether an independent inquiry would be held. The Minister set out the chain of events, stated it had not been proven that the drug causes malformation, no discussions on compensation had been had and he did not feel an inquiry would be helpful. A series of additional parliamentary questions and a debate followed until 1978 when the last of the HPTs was withdrawn from the market.
Dec 1977/ Jan 1978	**Primodos discontinued in the UK (no HPTs remain authorised in UK)**
1978	The London Programme - "Primodos: The Secret Drug Scandal" aired Cumorit discontinued in Spain
Feb 1978	Formation of the Association of Children Damaged by HPTs (membership of ~700 families)
March 1978	Schering decides Duogynon in any form will not be recommended as pregnancy test and pregnancy must be ruled out before taking it. Package inserts are modified and doctors informed. Schering lawyers say about UK action: "in the case of Primodos we do not believe there is any justifiable grounds for any causal link. However, in the opinion of our English staff and our consultants, Schering AG and / or SCL might be accused of lack of due diligence in informing medical doctors ever since we deleted the 1970 pregnancy test indication"

	and “the scientists of Pharmaceutical Division management still consider unproved the causal relationship between the occurrence of malformations and taking Duogynon, but on the other hand they are unable to prove the contrary.”
April 1978	CSM takes the decision not to notify mothers identified in the Maternal Drug Histories study that they had been given a HPT because its studies are conducted on the basis of strict confidentiality to protect participants, to ensure continuing co-operation with its work, and because it would be unethical to make any direct approaches to the mother or their offspring. Schering reports on informal talks with Bill Inman and claim that he destroyed/modified material on which his investigation the CSM study investigation was based, to make it impossible to trace the individual cases included in the study and prevent individual claims from using this material.
May 1978	Secretary of State gives personal view in a Parliamentary Question reply that he considers the reaction of the CSM was slow, but that was because it had to set up a new system under the Medicines Act and because the government is probably not backing up the work of the Committee adequately at that stage
July 1978	Dr Gal sends “a review of evidence implicating HPTs” to Secretary of State which placed in the House Library Duogynon remains licenced in 85 countries
August 1978	Schering specifies that, in addition to Germany, oral and/or parenteral Duogynon for secondary amenorrhoea is still on the market in 84 countries including the following European countries: – Italy (both forms) – Switzerland (both forms) – Belguim (both forms) – France (both forms) – Greece (both forms) – Austria (both forms) – Finland (parenteral) – Sweden (parenteral)
Sept 1978	SCAR and CSM consider Dr Gal’s review. CSM conclusions are provided to the Secretary of State

	Duogynon discontinued in Germany and replaced by Cumorit for secondary amenorrhoea.
Oct 1978	Symposium on HPTs organised by the West German Federal Heath Office and attended by global experts – concluded that HPTs for diagnosis of pregnancy must continue to be questioned; treatment of secondary amenorrhoea with HPTs should be at least 8 weeks post LMP and after excluding possible pregnancy
Dec 1978 / Jan 1979	Further warning from the FDA against use of HPTs in the first 4 months of pregnancy
1979	European network of population-based registries for the epidemiologic surveillance of congenital anomalies (EUROCAT) established Duogynon available as Cumoril in Italy
Dec 1979	WHO conference "The Effect of Female Sex Hormones on Foetal Development": recommends HPTs no longer used since their benefits and efficacy are questionable
Jan 1981	Schering injunction to ban "the Primodos Affair" TV programme – still in place
1982	Legal challenge fails in UK. Proceedings discontinued at the request of the plaintiffs, Judge Bingham stated "evidence would have to be very strong for a new trial"
1988	Enforced ban of HPTs in India
1990	Introduction of the International Conference on Harmonisation of Technical Requirements of Pharmaceuticals for Human Use (ICH) to provide a platform for international cooperation and consistency of approach to drug development
1999	Legal requirement for all medicines to have patient information leaflets
2005	CSM replaced by Commission on Human Medicines (CHM)
2008 – Oct 2014 and agreement to do HPT review by PS(LS)	
From 2008	An individual who considers their life to have been adversely affected by HPTs enters into extensive correspondence with MHRA and Ministers over HPTs and concerns that their mother's use of Primodos during pregnancy was the cause of their disabilities. Over the course of several years pages from a dossier of documents were provided to MHRA and a number of enquiries were made under FOI. Two meetings with MHRA were hold in Dec 2010 and Jan 2011 to discuss their concerns in more detail. The MHRA replied to all queries to the best of its ability given the limited historical data held by the Agency on HPTs.

25 October 2010	Meeting between PS(Q) and MHRA (Policy/VRMM)/DH
April 2012	Representative from MHRA searches National Archives for information on Primodos.
April 2012	Yasmin Qureshi MP submitted an Early Day Motion (2795) to the House calling for a public inquiry. Her concerns are that: a) no official warnings were issued until eight years after the first reports indicated possible dangers b) some doctors continued to prescribe the drugs for pregnant women after official warnings from the Committee on Safety of Medicines c) DH has continuously rejected requests for an inquiry into these matters.
July 2012	Representatives from MHRA meet Ester McVey (Minister for Disabled people) to discuss HPTs
16 July 2013	Yasmin Qureshi MP asks topical question in House of Commons asking for meeting with PS(H) to present evidence on what has happened, to which PS(H) agreed
8 Jan 2014	Yasmin Qureshi MP meets in person with Dr Dan Poulter (PS[H]) and a representative from the MHRA to discuss the alleged association between the use of Primodos, and the occurrence of congenital anomalies in the offspring. PS(H) asks MHRA to provide a summary of findings from the historical evidence on HPTs
March 2014	MHRA completes review of the key epidemiological studies which concludes “the data are not sufficient to conclude that there is a causal association between the use of Primodos (or any HPT) and congenital abnormalities”; MHRA provides copies to PS(H), PS(Q) and Yasmin Qureshi MP and publishes a copy on the MHRA website.
19 Mar 2014	Yasmin Qureshi MP states at PMQs there has never been a public inquiry or compensation for the victims of HPTs, and asks the Prime Minister to meet her, her constituent, and a representative of the patients group to discuss this. The PM states he is very happy to look at the case that she raises, and get back to her about it.
14 May 2014	All-Party Parliamentary Group (APPG) on HPTs formed by Yasmin Qureshi MP, who latterly became Chair of the APPG
17 June 2014	Yasmin Qureshi MP presents a petition with more than 400 signatures in the House requesting that the House of Commons urges the Government to set up an Independent Public Inquiry.
18 June 2014	Yasmin Qureshi MP asks the PM during PMQs if he will meet more than 50 members of the patient group visiting Parliament that day, look at the documents they have produced, which they claim show that the then medical community knew that the drug was causing deformities in babies and nothing was done about it; and consider a public

	inquiry. The PM states that he cannot meet them is very happy to have another conversation with her about what can be done and to understand what more can be communicated.
18 June 2014	APPG on HPTs meeting to discuss their concerns over Primodos and the need for a Public Inquiry
1 July 2014	Sky News wrote to the PM with its concerns about Primodos and drawing attention to Yasmin Qureshi MP's calls for a public enquiry; the PM responded to say he did not believe that a public inquiry is required at this time, that ministers are always prepared to review any new evidence that arises and he encouraged Sky to forward any documents they consider were not included in the recent MHRA review.
8 July 2014	Yasmin Qureshi MP, Nick de Bois MP and Jacob Rees-Mogg MP called for a Backbench Business Committee debate to discuss the motion that between 1953 and 1975 thousands of children were born with deformities because their mothers took Primodos. They asked for full disclosure of the documents relating to its use and want "the Secretary of State to set up an independent panel to examine these documents."
9 July 2014	Yasmin Qureshi MP meets with the Prime Minister to discuss her concerns about Primodos and requests an independent public enquiry. YQ alleges the MHRA is withholding information [but MHRA released everything it held on HPTs (although what information was held was very limited)]
23 Oct 2014	Backbench Business Committee debate in House of Commons takes place. PS(LS) agrees to an independent review of the papers and all the evidence: Oral Hormone Pregnancy Tests - Backbench Business Committee debate on 23rd October 2014
Nov 2014 – Nov 2017 and publication of the HPT EWG report	
13 Nov 2014	Commission on Human Medicines (CHM) informed of a Ministerial commitment to convene a panel of independent experts to review of all the evidence relating to use of HPTs and a possible risk of birth defects.
2 Dec 2014	MHRA contacts other EU Member States to request information on the HPTs which were available, any communications or regulatory action taken with respect to HPTs and congenital abnormalities and details of any current or ongoing reviews of or interest in HPTs in each MS.
9-12 Dec 2014	MHRA contacts companies whose predecessors marketed HPTs, Royal Colleges and Dame Valerie Beral to request submission of any information or data held on HPTs and a possible association with congenital abnormalities
11 Dec 2014	CHM is updated on the government's commitment to convene a panel of independent experts to review of all the evidence relating to use of HPTs and a possible risk of birth defects and the revised draft terms of reference , i.e.:

	a. To consider all available evidence on the possible association between exposure in pregnancy to HPTs and congenital abnormalities in the child, including consideration of ***any*** potential mechanism of action b. To consider whether the Group's findings have any implications for currently licensed medicines in the UK or elsewhere and to make recommendations
January 2015	MHRA engages a professional researcher to locate and obtain copies of all relevant archived materials related to HPTs from the National Archives at Kew
19 Jan 2015	PS(LS) meets with Chair and Vice-Chair of APPG on HPTs to discuss the scope of the review and possible membership of the EWG. During the meeting. the Chair of the APPG proposed the inclusion of Dr David Healy as a member of the EWG.
19 Feb 2015	Dr Ailsa Gebbie appointed by CHM as Chair of the EWG
23 Feb 2015	Further to the meeting with PS(LS), Yasmin Qureshi MP and Nick de Bois MP on 19th Jan 2015, a meeting had been arranged for 11 Mar 2015 between Yasmin Qureshi MP, Nick de Bois MP, Ailsa Gebbie (the Chair of the EWG) and the Chair of the Association. The meeting was cancelled on legal advice that a meeting between the Chair of the Expert Group and the Chair of the Association could be perceived to compromise the impartiality of the Chair of the expert group and the integrity of the review.
24 Feb 2015	Graeme Morrice MP asks what progress has been made in "setting up the inquiry" and for assurances that the inquiry will be fully comprehensive, transparent and independent. PS(LS) stated the chair had been appointed the terms of reference for the inquiry are clear and comprehensive. He clarified it was not a judicial inquiry; it is a medical inquiry looking at the evidence.
11 Mar 2015	Secretariat to the EWG sends invitations to potential members (including 3 lay representatives), invited experts and observers. The Chair of the Association is invited to attend meetings of the EWG as an observer.
24 Mar 2015	PS(LS) endorses the launch of a public call for evidence, proposals for further engagement with Bayer regarding provision of data for the review, and the formation of an EWG (and its draft Terms of Reference), i.e.; a. To consider all available evidence on the possible association between exposure in pregnancy to HPTs and congenital abnormalities in the child, including consideration of any potential mechanism of action; b. To consider whether the Group's findings have any implications for currently licensed medicines in the UK or elsewhere and; c. To make recommendations

25 Mar 2015 (until 30 Jun 2015)	MHRA launches public call for evidence on HPTs which is published on MHRA website accompanied by a Press Release. MHRA wrote to the Chair of the Association to provide further details of the review and inform her the call for evidence was live; a former Chair of the Association and the Devolved Administrations were also informed via e-mail.
25 Mar 2015	Representatives from MHRA spoke with the Chair of the Association by telephone. During the call, the Chair of the Association suggested Mr Dobrik be invited as a lay representative to provide procedural advice,and expressed concern over invitation of Sir John Burn (who is a colleague of Prof Steve Robson, who previously compiled evidence for scoping studies on HPTs). MHRA confirmed that members of the Association need not present their evidence in person (and could provide it in writing) and invited the Association to submit their documents as evidence.
27 Mar 2015	YQ writes to George Freeman to outline her dissatisfaction with a number of issues including: 1. The fact that the “independent panel” is being advised by MHRA lawyers 2. The close involvement of MHRA in setting up the panel, seeing this as a conflict of interest in view of her understanding that the panel would be investigating the culpability of CSM The impartiality of the Panel in view of the above
18 May 2015	A planned meeting between the Chair of the Association, Mr Dobrik and the MHRA is postponed (due to its proximity to the general election) and rescheduled for 18th Aug 2015.
11 Jun 2015	MHRA publishes article in ‘Drug Safety Update’ to draw attention to the call for evidence.
23 Jun 2015	MHRA meets with Bayer to discuss the provision of data for the review. Bayer confirmed they have access to scientific material relating to Primodos from 1982 litigation, was cataloguing this and would make these available to MHRA by autumn 2015.
18 Aug 2015	At their request MHRA meets with the Chair of the Association and Mr Dobrik to discuss the role of both on the EWG, and the terms of reference for the review. Following this, on 20 Aug Mr Dobrik accepted an invitation to attend meeting of the EWG as an invited expert.
Aug-Sep 2015	Chair of the Association provides 31 files from the Landesarchiv Berlin
16 Sep 2015	CHM updated on the proposed membership of the EWG and the interests declared by those invited to participate in it. CHM endorsed the membership.

15 Sept 2015	PS(LS) confirms the terms of reference in a letter to APPG. In the same letter, the Minister confirmed that: “it is important to review the scientific evidence to establish whether there is any causal association between use of HPTs and subsequent birth defects in the child.”
14 Oct 2015	First meeting of the EWG of the CHM on HPTs, which agreed a number of topics to cover in future meetings, including: • Pharmacology and Pharmacokinetics, with a particular focus on the constituents of the two mostly widely-used products, Amenorone Forte and Primodos (ethinylestradiol, [EE] with ethisterone or norethisterone acetate [NET]); • Toxicology and studies of teratogenicity, with a particular focus on data from animal studies of single- and repeat-dose toxicity, reproductive toxicity and genotoxicity; • Clinical trials and/or published reports of the use of progestogen/oestrogen for pregnancy testing; • Epidemiological evidence, including data from prospective and retrospective studies of the outcomes of pregnancy and exposure to HPTs; • Spontaneously-reported ADR data, individual case reports and case series involving adverse effects of HPTs on pregnancy, including reports from the Yellow Card scheme in the UK and other ADR reporting systems worldwide, information on individual cases, published cases and case series. The *EWG also made some amendments to the terms of reference:* • *To consider all available evidence on the possible association between exposure in pregnancy to HPTs and adverse outcomes in pregnancy (**in particular congenital anomalies, miscarriage and stillbirth**) including consideration* of any potential mechanism of action; • To consider whether the Group's findings have any implications for currently licensed medicines in the UK or elsewhere; • ***To draw any lessons for how drug safety issues in pregnancy are identified, assessed and communicated in the present regulatory system and how the effectiveness of risk management is monitored;*** • To make recommendations.
15 Oct 2015	PS(LS) meets with APPG on HPTs
16 Oct 2015	CHM informed of and endorsed the revised terms of reference proposed by the EWG

16th October 2015	Mrs Lyon is asked if the 4th December was suitable for families to attend the 2nd meeting of the EWG.
23rd October 2015	Mrs Lyon agrees the date of 4th December for families to present their experiences to the EWG
28th October 2015	Mrs Lyon informed of meeting time – 10am – 2pm
28th Oct 2015	Mrs Lyon questions whether the meeting will be long enough for the EWG to hear the families' stories [NB room could not be booked beyond 2pm and some families could not get there earlier than 10am as travelling long distances].
2 November 2015	MHRA informs Mrs Lyon that people from its Patient and Public Engagement group will be there to assist members in advance and on the day and asked if there was any special guidance that would be helpful to them.
17 – 20 November 2015	Mr Dobrik at MHRA to review documents for 2nd EWG meeting – assisted throughout by MHRA staff and provided with laptop and refreshments
18 November 2015	Mrs Lyon asked what format members would prefer to present to the EWG
23 Nov 2015	Mrs Lyon advises MHRA that members would prefer to speak to the EWG panel individually and she has informed them they will have a maximum of 15 mins each.
27 Nov 2015	Mrs Lyon sent guidance document outlining what would happen on the 4th Dec and what support there will be from MHRA staff. Families informed they will have 10-15 mins to present to the panel.
1 Dec 2015	Mrs Lyon informed that a room will be devoted to the families and refreshments organised, including lunch. Mrs Lyon given options for how families may prefer to present.
4 Dec 2015	Second meeting of the EWG of the CHM on HPTs, during which: • The EWG endorsed the revised terms of reference • Dr David Healy (who was proposed as member of the EWG by the Chair of Association) presented on the topic "Spontaneous reporting systems and their strengths and limitations, particularly with respect to detecting/identifying birth defects and adverse effects on the pregnancy" to the EWG. • The EWG considered spontaneously-reported adverse drug reaction (ADR) cases (from the Yellow Card scheme, other regulators worldwide, and a summary of litigation cases) and individual case reports involving adverse effects of HPTs on pregnancy; the Group made a number of recommendations for further work in this area. • The EWG heard directly from 13 people or families who feel they have been affected by HPTs about their experiences.

18 Dec 2015	Complaint logged by the Chair of the Association raising the following concerns: i. Lack of opportunity to contribute to discussions of the EWG in her role as observer; ii. David Healy's involvement in the EWG as a visiting expert rather than a full member; iii. Conflicts of interest of invited expert Dr Laura Yates and interests allegedly not declared to Expert Committee Support by invited expert Prof Dr med. Christof Schaefer; iv. Lack of translation (from German to English) of documents provided by the Association for inclusion in the review; v. Lack of presentation of documents provided by the Association to the EWG; vi. The (poor) treatment of the members of the Association (and their families) who visited 151 BPR on 4th December to talk to the EWG about their experiences and lack of time to do so; members had felt intimidated and rushed vii. Insufficient time to review the papers before each meeting. MHRA responded to these concerns on 29th Dec 2015; in an email of 6th Jan 2016 the Chair of the Association did not accept most of the explanations provided.
21 January 2016	Lord Kennedy of Southwark raised a question in the House of Lords on the timeframe for the inquiry into the safety of hormone pregnancy tests, and when they expect the report to be published. PS(DH) clarified that the expert working group met twice in 2015 and a number of further meetings will be held in 2016. He also stated a report of the group's findings will be published once the review is complete, which is expected before the end of the year. A number of followup questions followed.
30 March 2016	MHRA responds to the points raised by the Chair of the Association on 6th Jan.
1 -4 April 2016	ECS invite Dr Vargesson to present his data to the EWG at their meeting in April where non-clinical data will be considered. Dr Vargesson says he is unable to attend but would be happier to do a later meeting.
7 April 2016	Mrs Lyon acknowledges it was not the intention of MHRA to cause distress to members but the lack of time to share experiences did do so and could have been avoided. Also reiterates points raised previously about lack of time to consider documents.
8 - 12 April 2016	MHRA asks if Dr Vargesson would consider sending MHRA data to be taken into consideration in the review. Dr Vargesson says he thinks it would be better to discuss, and that the data are currently unpublished but that he plans to publish over the summer of 2016. MHRA asks Dr Vargesson if he could supply a written summary for the review. Dr

	Vargesson thinks best approach is to get the work published (summer/autumn) or sent to a journal and provide us with the manuscript. MHRA thanks Dr Vargesson for his offer to share the manuscript.
25 Apr 2016	Third meeting of the EWG of the CHM on HPTs. The EWG considered whether there may be a plausible mechanism by which HPTs may cause congenital anomalies or early interruption of pregnancy (miscarriage), based on presentation of the following evidence: a) normal embryonic and fetal development and how this may be affected by known teratogens b) the pharmacology of EE/NET c) the pharmacokinetics and pharmacodynamics of EE/NET in the mother and fetus. d) toxicological data (animal and human) from studies which have investigated whether EE and NET have toxic effects on the developing fetus. The EWG was also presented with an update on spontaneously-reported ADRs. The EWG noted at this meeting that Dr Neil Vargesson had been invited to present his work to the Group but, being unable to attend this meeting, would instead be asked to a future meeting.
7 May 2016	Dr Vargesson states his intention to get his work written up and submitted over the summer, and to share the manuscript or a detailed summary of the findings if he cannot attend a later meeting.
27 May 2016	MHRA staff attend office of Arnold and Porter LLP to retrieve relevant data for the review from litigation paperwork
22 June 2016	MHRA invites Dr Vargesson to the 18th October meeting
30 June – 1 July 2016	MHRA follows-up on invitation to Dr Vargesson. Dr Vargesson accepts invitation. MHRA confirms details and requests copy of presentation a week before the meeting. Dr Vargesson agrees to submit slides in advance as long as it has been submitted to a journal.
5 July 2016	The APPG writes to the Chair of the EWG setting out its concerns with regard to the EWG, i.e. selection of panellists and conflicts of interest, inclusion of all evidence, and accountability of the inquiry. Dr Gebbie responds to these concerns in writing.
11 Aug 2016	Fourth meeting of the EWG of the CHM on HPTs, during which the EWG: • Noted an updated schedule of information held on HPTs and updated chronology of events (including usage of HPT products) • Noted and discussed a further analysis of spontaneous reports with HPTs

	The EWG heard presentations from Dr Diana Wellesley on 'Current position and options for registries in pregnancy and congenital anomalies', from Prof Helen Dolk on 'Pharmacovigilance for medication safety in pregnancy' and from the following visiting experts: • Ms Rachael Williams (on 'Using the Clinical Practice Research Datalink (CPRD) to collect data on medicines in pregnancy and congenital anomalies') • Ms Sarah Stevens (on 'Future direction - registries of pregnancy and congenital anomalies') • Dr Ulla Wandell Liminga and Professor Corinne de Vries (on 'Good Vigilance Practice guidance') The EWG noted that Dr Vargesson would present at the next meeting of the EWG and commented that it would be helpful to see his study data in advance of the meeting.
13 July 2016	MHRA sends the EWG all data submitted through the public call for evidence, the complete set of papers from the 3rd and 4th meetings, files from the TNA, all supporting references etc
21 Sept 2016	MHRA sends all references and study reports supporting the paper on non-clinical data to EWG.
11 Oct 2016	Dr Vargesson confirms he won't be leaving copy of slides as data are confidential
13 October 2016	Dr Vargesson agrees to send a PDF version of the talk [no PDF was received]
13 Oct 2016	Backbench Business Committee debate in House of Commons, regarding APPG's concerns that i) the terms of reference doesn't cover regulatory failings; ii) some panel members have conflicts of interest; iii) not all evidence is being considered; iv) the review does not have the trust and confidence of the victims for whom it was set up. Commitment made to look into the concerns and meet.

18 Oct 2016	Fifth meeting of the EWG of the CHM on HPTs, during which the EWG:
	• considered epidemiological evidence for a possible association between norethisterone acetate and ethinylestradiol and an adverse outcome in early pregnancy, including:
	  ○ HPTs and congenital anomalies
	  ○ Oral contraceptives s in pregnancy and congenital anomalies
	  ○ Norethisterone acetate and/or ethinylestradiol in women with threatened or recurrent miscarriage and risk of congenital anomaly
	  ○ Norethisterone acetate/ethinylestradiol in early pregnancy and risk of miscarriage

	• noted a work plan for further ADR analysis, and disproportionality from UKTIS • considered a genetic testing scoping paper • considered translation of excerpts from Landesarchiv Berlin files, provided by German member of the EWG, Prof Axel Heep • Heard a presentation from Dr Neil Vargesson on 'New pre-clinical data on the effects of HPTs', comprising preliminary findings from small studies looking into the effects of norethisterone acetate and ethinylestradiol on blood vessel and limb development using zebrafish and chick embryo models, respectively • Considered an update on evidence from pre-clinical data relevant to a possible association between NET and EE and adverse effects on pregnancy or the developing fetus • Considered evidence for disruption of the vasculature of the developing pregnancy by HPTs • Noted an apology from the Chair of the Association for the way in which members of the EWG had been referred to in the Westminster debate of 13 Oct 2016 • Members of the EWG provided advice on the meeting conclusions and recommendations (invited experts and observers did not attend this part of the meeting, as per the definition of participation for the EWG)
21-22 Nov 2016	Someone who considers that their life to have been adversely affected by HPTs brings their dossier of evidence to the MHRA offices, where they are scanned in their entirety over the course of 2 days. The scans are provided to the EWG
31 January 2017	MHRA representative attended conference on HPTs at Cambridge University, organised by Dr Jess Olszynko-Gryn
17 February 2017	Invitation to Dr Olszynko-Gryn to present at the meeting of the EWG on 24th April.
20 Feb 2017	EWG provided with full English translations of all documents from the Landesarchiv Berlin
21 Mar 2017	Sky News documentary 'Primodos: The Secret Drug Scandal' broadcast on Sky Atlantic (and on 'Sky News' the following day). MHRA attended.
27 Mar 2017	Sixth meeting of the EWG of the CHM on HPTs, during which the EWG: • noted feedback on the conference on HPTs at Cambridge University on 31st January 2017 and the screening of the Sky News documentary in the House of Commons on 21st March 2017 • considered a re-analysis of the epidemiological evidence for a possible association between HPT use and congenital anomalies

	• considered a further analysis of spontaneous reports with HPTs • considered the possible effect of norethisterone acetate /ethinylestradiol on the developing fetus: evidence from pharmacological data • heard a presentation from the MHRA on valproate and risks in pregnancy (at request of Mr Dobrik) • Members of the EWG provided advice on the meeting conclusions and recommendations (invited experts and observers did not attend this part of the meeting, as per the definition of participation for the EWG)
31 March 2017	MHRA contacted Dr Vargesson to ask if he was in a position to provide a peer-reviewed manuscript of his work for consideration by the Group at their meeting on 24 April. Dr Vargesson informs MHRA that he conducted some additional experiments following feedback from the EWG meeting in October 2016, is finishing writing the manuscript and aims to submit it to a peer-reviewed journal within 2-3 weeks.
6 April 2017	Bayer requests meeting.
19 April 2017	Rescheduled meeting with APPG and LO'S cancelled due to availability issue
24 Apr 2017	Seventh and final meeting of the EWG of the CHM on HPTs during which the EWG: • Heard a presentation from Dr Olszynko-Gryn on "The Contested History of Hormone Pregnancy Tests" • Heard a presentation from the Chair of the Association on Documents from the Landesarchiv Berlin and the importance of the pre-clinical work by Dr Vargesson in chick embryos and zebrafish (previously presented to the Group). • Noted the updated schedule of documents held and the updated chronology of events • Considered lessons learnt with respect to identifying, assessing and communicating drug safety concerns in pregnancy • Heard a presentation from Prof Helen Dolk (with Prof Pat Doyle and Dr Laura yates) outlining proposals for a pregnancy pharmacovigilance system • Members of the EWG provided advice on the meeting conclusions and recommendations (invited experts and observers did not attend this part of the meeting, as per the definition of participation for the EWG)
8 May 2017	Meeting with Bayer to provide a progress update, discuss the Bayer perspective and agree next steps.
24 July 2017	Meeting with HPT EWG members to discuss first draft of the report

31 July 2017	MHRA requests an update on publication of his work from Dr Vargesson
31 July 2017	Dr Vargesson informs MHRA he has conducted further studies and will submit the paper for publication within the next 2 weeks
1 Aug 2017	Re-scheduled meeting LO'S, Yasmin Qureshi MP, Hannah Bardell MP and the Chair of the Association. MHRA not present
8 August 2017	Dr Vargesson informs MHRA he is hopeful of getting the paper submitted in the next fortnight and that it will be a few months before formal acceptance.
17 August 2017	Dr Vargesson informs MHRA the manuscript has been submitted but he is unable to provide the EWG with a copy due to Journal rules.
17 August 2017	Mrs Lyon invited to attend meeting on 16th October with families to feedback on the HPT report
20 August 2017	Mrs Lyon confirms attendance at the feedback meeting on 16th October.
22 August 2017	Draft HPT EWG recommendations sent to Mrs Lyon and Mr Dobrik for their review
25 August 2017	TC MHRA, HPT EWG toxicologist and Dr Vargesson to discuss progress on his work and publication before finalisation of the EWG report.
29 August 2017	Meeting MHRA, Mr Dobrik and Mrs Lyon to discuss the recommendations.
31 August 2017	MHRA invites Mrs Lyon and Mr Dobrik to make a statement to the CHM at their meeting on 6th October
31 August 2017	MHRA asks Bayer to clarify statements in historical documents from the Landesarchiv Berlin potentially relating to clinical trial data on Primodos that was not submitted for the review.
7 Sept 2017	CHM provided with a verbal orientation on the HPT review in preparation for consideration of the report at their October meeting
8 September 2017	Bayer confirms neither they nor their German counterparts have been able to find any trial data on Primodos in the archives.
10 September 2017	Meeting with families to present the HPT EWG report planned for 16th October cancelled at short notice due to the need for the EWG to agree the updates proposed by the CHM.
12 September 2017	HPT EWG members informed of Bayer's response to the question on clinical trial data and asked for their views on whether action was needed and whether the report needed updating.

15 September 2017	HPT EWG members confirm no action or updating of report required.
15 September 2017	Draft HPT EWG report couriered to Mrs Lyon
19 September 2017	Informed Mrs Lyon that we had investigated with Bayer whether there was RCT data for Primodos and the outcome. Mrs Lyon thanked us for trying
20 September 2017	Updated report sent to EWG for agreement. Further updates to the report made in response to EWG comments.
21 September 2017	Draft HPT EWG report sent to CHM for consideration at their meeting on 6th October
21 September 2017	Submission to LO'S to inform of conclusions and recommendations of the EWG, its consideration by CHM in October and next steps for publication of the report after the October CHM meeting.
27 September 2017	LO'S noted submission with no comments.
28 September 2017	LO'S content with providing WMS
6 October 2017	CHM consideration of the draft HPT EWG report. Mrs Lyon invited to attend to provide her views on the process and the report. Mr Dobrik sends his apologies on the day due to family illness. The CHM fully endorsed the conclusions of the report and suggested some changes to the draft to ensure that the scientific process and language used in the report was as clear and as digestible as possible for non-experts, and to make it more accessible. The CHM also proposed some additional recommendations.
12 October 2017	LO'S writes to Yasmin Qureshi MP re sharing HPT EWG report and offering to meet after its publication
12 October 2017	Mrs Lyon informed of the postponement of the feedback meeting with families.
16 October 2017	Original date planned to meet with the families and hold press briefing [subsequently took place on 15th November].
27 October 2017	CHM sent updated EWG report for consideration at the 2nd-3rd November meeting.
2–3 October 2017	HPT EWG report endorsed by CHM. The conclusion on the data was identical to that in the report that was considered by CHM in September.

6 November 2017	Submission to LO'S requesting acceptance of the CHM advice and approval of the Written Ministerial Statement
9 November 2017	LO'S confirms MHRA can invite families to the meeting on 15th November
10 November 2017	MHRA informs Mrs Lyon of the meeting and asks her to tell the families. Mrs Lyon replies to say 2 working days' notice is unacceptable. Mrs Lyon says she will wait to hear from ECS before contacting members. ECS says it will feedback Mrs Lyon's concerns with regard to the meeting with families and get back to her on Monday 13th November. Mrs Lyon also questions if she will have a final copy of the EWG report before the meeting.
13 Nov 2017	ECS confirms the time and date of the meeting with families with Mrs Lyon and that Mrs Lyon will not have a final copy of the report before the meeting but that they will all have copies to take away with them. Mrs Lyon asks if the conclusions have changed. Mrs Lyon informed that the report was updated to take into consideration the deliberations of CHM. Mrs Lyon expresses disappointment at the short notice and the distress caused to the families.

14 Nov 2107	Mr Dobrik verbally agrees to attending the MHRA press conference and state his availability for interviews. He informs MHRA that he intends to make the following broad points:
	• The review was very thorough and took great care looking at the evidence.
	• Pleased that the investigation into Primodos also gave an opportunity to look at ways to safeguard future generations.
	• Will highlight:
	  ○ Enhanced collection of data.
	  ○ Use of new techniques to analyse data.
	  ○ Better co-ordination between the bodies collecting the data.
	• These recommendations will together make a great contribution to improving the safeguarding of future generations.
	
	He will not discuss the conclusions.

15 November 2017	Mr Dobrik informs MHRA he is unable to attend the press briefing due to family illness.
15 November 2017	LO'S writes to Yasmin Qureshi MP in response to her concerns over the review process including changes to the report requested by CHM.
15 November 2017	Re-scheduled meeting with families to discuss the conclusions and recommendation of the EWG report.

15 November 2017	Press conference. Yasmin Qureshi MP and Hannah Bardell MP arrived unexpectedly requesting access but were refused because they were not on the invite list. Later that day MHRA contact the MPs to organise a meeting with Dr Gebbie.
15 November 2017	Yasmin Qureshi MP and Hannah Bardell MP agree to a meeting and request possible dates.
15 Nov 2017 and publication of the HPT report – present day	
16 November 2017	Urgent Question from Yasmin Qureshi MP on HPTs: *To ask the Secretary of State for Health if he will make a statement on the recently published Report of the Commission on Human Medicines' Expert Working Group on Hormone Pregnancy Tests.*
17 November 2017	HPT EWG report published in the House, accompanied by written Ministerial submission, and uploaded to the CHM website.
17 November 2017	MHRA offers 22nd November to Yasmin Qureshi MP and Hannah Bardell MP
20 November 2017	MHRA follows up with Yasmin Qureshi MP and Hannah Bardell MP to confirm a date.
20 November 2017	Yasmin Qureshi MP confirms time and venue for APPG to meet Dr Gebbie on 22nd November.
21 November 2017	Meeting with Bayer to discuss MHRA plans for publication of the supporting data.
22 November 2017	Meeting APPG, Chair and statistician from EWG and MHRA to discuss the EWG review. Hannah Bardell MP could not make the meeting and so requested to meet Dr Gebbie separately.
22 November 2017	PMQ refers to Mr Dobrik to demonstrate the independence of the review. This line first came up in the Urgent Question but was not suggested as a response by the MHRA.
27 November 2017	Hannah Bardell MP requests meeting with Dr Gebbie.
28 November 2017	TC Bayer and MHRA to discuss confidentiality issues regarding publication of supporting evidence
6 December 2017	Meeting APPG, Minister and MHRA to discuss the HPT EWG review
12 December 2017	Requested information on congenital anomalies provided to Sharon Hodgson ahead of the debate on 14th December.
13 December 2017	Mrs Lyon forwards all correspondence with MHRA to LO'S
14 December 2017	Backbench Business Committee debate called by Mike Penning MP:

	• *"That this house regrets the terms of reference for the commission on human medicines expert working group on hormone pregnancy tests was asked to consider evidence on a possible association between exposure in pregnancy to hormone pregnancy tests and adverse outcomes in pregnancy, but the commission's report concluded that there was no causal association between the use of hormone pregnancy tests and babies born with deformities between 1953 – 1975, even though it was not asked to find a causal link;* • *Believes that the inquiry was flawed because it did not consider systematic regulatory failures of the committee on safety in medicines and did not give careful consideration to the evidence presented to it;* • *And calls on the government, after consultation with the families affected so they have confidence in the process, to establish a statutory inquiry under the inquiries act 2005 to review the evidence on a causal association between hormone pregnancy tests on pregnancies and to consider the regulatory failures of the committee on safety in medicines."*
16 November 2017	Urgent Question
19 January 2018	Mr Lyon phoned with some questions for MHRA on genetic testing recommendation.
19 January 2018	Hannah Bardell MP's office suggest 26th January to meet
23 January 2018	Hannah Bardell MP's office cancels due to a diary clash
24 January 2018	MHRA followed up with Mr Lyon asking for confirmation in writing on the issues raised. This is confirmed on 26th Jan.
26 January 2018	MHRA suggests 16 February to meet Hannah Bardell MP. Hannah Bardell MP's office suggests 23rd February, MHRA suggests 23 March - neither dates are suitable.
31 January 2018	All evidence that was provided to MHRA and the CHM EWG for the purposes of the review, together with all the supporting documentation is uploaded onto the CHM website (https://www.gov.uk/government/publications/report-of-the-commission-on-human-medicines-expert-working-group-on-hormone-pregnancy-tests)
5 February 2018	MHRA replies to Mr Lyon, informing him that the referral letters for families on the CHM website had been revised to make them more user-friendly and answering his other questions about the process.
6 February 2018	Hannah Bardell MP's office suggests 29 March.
6 February 2018	MHRA sends letters to all genetic testing centres in the UK to heighten awareness of and provide background to incoming requests for testing.
7 February 2018	Hannah Bardell MP's office confirms 29th March. MHRA organises travel and accommodation for 2 people

13 February 2018	Submission to LO'S requesting agreement to chair a Cross-Sector Steering group to oversee implementation of the HPT recommendations
13 February 2018	Publication of work of Dr Vargesson's group in Nature Scientific Reports on the effect of the components of Primodos on the development of zebrafish embryos.
15 February 2018	CHM discussion of the Vargesson zebrafish publication. CHM considered that the specialist nature of the work required establishing an ad hoc expert group to consider the robustness of the data and any implications it may have on the conclusions of the HPT EWG.
23 February 2018	Mr Lyon contacted MHRA to tell us that some members of the Association had been told they did not require a genetic test.
27 February 2018	MHRA asks for details of the centres that have refused a request for testing.
14 March 2018	Submission to LO'S seeking views on proposed next steps for reviewing the of Dr Vargesson's study
15 March 2018	LO'S content with an ad hoc CHM group but requests options for an independent review in parallel.
17 March 2018	Mr Lyon provides details of the test centres.
27 March 2018	Hannah Bardell MP's office cancels meeting due to Chamber business.
28 March 2018	Submission to LO'S with options for independent review of Dr Vargesson's work
28 March 2018	MHRA offers 25th April to Hannah Bardell MP's office.
9 April 2018	LO'S states his preference for an Article 5(3) referral in Europe
9 April 2018	MHRA informs Mr Lyon that Dr Wellesley (clinical geneticist on the EWG) has offered to speak to the individual genetic testing centres
10 April 2018	Hannah Bardell MP's office confirms 25th April to meet but has to cancel the same day.
13 April 2018	Hannah Bardell MP's office offers 18th May. Dr Gebbie cannot make the proposed time due to clinical commitments.
19 April 2018	CHM consideration of proposed terms of reference and membership of an ad hoc expert group to consider the zebrafish data.
24 April 2018	MHRA requests an Article 5(3) referral in Europe on the zebrafish work

27 April 2018	MHRA sends a letter from Dr Wellesley and Dr Yates (members of the original HPT EWG) to all testing centres encouraging them to accept all members of the Association for testing.
9 May 2018	Professor Alan Boobis invited to Chair a new Expert Group (EG) of toxicologists to review the research of Dr Vargesson's group
22 June 2018	LO'S updated on progress in establishing ad hoc expert group to review zebrafish research and commencement of EU review of the same research. LO'S asked to approve the final terms of reference of the CHM expert group and sign the letter updating the APPG
28 June 2018	LO'S requests that the terms of reference for the EG are identical to those for the EMA review
July 2018	Correspondence with Dr Vargesson over availability for attending a meeting of the EG
10 July 2018	LO'S informs APPG about the CHM EG review of Dr Vargesson's study, the terms of reference for the review and the parallel examination of the data by the EMA's Committee for Medicinal Products for Human Use (CHMP)
19 July 2018	CHM endorse terms of reference for the EG
23 July 2018	First meeting of the cross-sector steering group on implementation of the EG recommendations for safer use of medicines in pregnancy and lactation
23 July 2018	Baroness Cumberlege proposes to LO'S that a member of the review team has observer status at the EG and CHMP meetings to discuss the zebrafish study.
31 July 2018	MHRA confirms with the Cumberlege review team that observer status is fine and follows up with further additional information.
16 August 2018	Date of zebrafish EWG set for 5th October
14 Sept 2018	Assessment report sent to all members of EG and Dr Vargesson
5 October 2018	CHM EG meets to consider the zebrafish data. After careful discussion of the findings, including with the lead researcher, the Group unanimously concluded that, while well conducted, there are no implications for clinical use of medicines currently on the market which containing norethisterone and ethinylestradiol.
8 October 2018	Second meeting of the cross-sector steering group on implementation of the EG recommendations for safer use of medicines in pregnancy and lactation
9 October 2018	The Safety Working Party (the non-clinical toxicology expert group that advises the CHMP) met to consider the zebrafish study and conclude that due the multiple limitations the results of the zebrafish study do not add to the current

	knowledge regarding adverse events in early pregnancy in human. As such, the presented results do not have clinical implications and the conclusion, as stated by the Expert Working Group of the MHRA on HPTs, remains valid.
11 October 2018	The findings and advice of the EG are reviewed and endorsed by the Commission on Human Medicines.
16 October 2018	CHMP considers the advice of the SWP on the zebrafish study
19 October 2018	Minutes of the CHM Expert Group published on CHM website
26 October 2018	CHMP article 5(3) assessment report published on the EMA website
29 October 2018	CHM Expert Group, Mrs Lyon, Professor Vargesson and Dr Macleod sent final minutes of the Group's meeting and the CHMP assessment report.

Annex C: Detailed points and a Timeline for Q1 on Abdominal and Vaginal Pelvic Mesh

2010

- **May:** As part of our continuing market surveillance role, we wrote to urogynaecology mesh manufacturers known to have mesh on the UK market, stating we had received a small but increasing number of reports (see below) from patients who had experienced complications such as pain, infection and erosion. We requested and examined a range of information relating to adverse events and pre and post market information. Whilst a small number of women had experienced distressing effects, the current evidence shows that when these products are used in appropriate treatment pathways, they can help with the very distressing symptoms of stress urinary incontinence (a list of symptoms is given by NHS Choices). We found no evidence from the information provided that suggested the devices did not comply with the requirements within the Medical Device Directive. No regulatory action was taken however we continued to keep this area under review as part of ongoing post-market surveillance and took the next step.
- **May:** We contacted known clinical experts about our concerns with reports we had received from patients who had experienced complications with mesh asking them about their experience of using mesh in urogynaecology. Responses indicated that patient selection, training and informed patient consent were at the heart of the matter.

2011

- **March**: In response to increasing number of adverse incident reports (42 reports in 2010 from the use of slings for female Stress Urinary Incontinence (SUI) to MHRA by the public, manufacturers and users, we hosted a workshop to better understand the use of these SUI devices and complications associated with their use. Chaired by Professor Abrams (then Director of Bristol Urological Institute), representatives included the Royal College of Obstetricians and Gynaecologists (RCOG), manufacturers, and National Institute for Health and Care Excellence (NICE). A summary of the discussion and recommendations were published in the European Urology Journal. It concluded:

  "The clinicians at the meeting concluded that all parties need to ensure that they fulfil their obligations to optimise patient safety and to ensure that patients only receive devices that are likely to produce a significant improvement in their incontinence and to deliver a satisfactory quality of life. The key points to improving the current situation when a new device is introduced into the market are as follows:

  - *Adequate clinical evidence should be available to support its safety and efficacy.*
  - *A standard for training and mentorship for the use of a significantly new device should be produced by the professional organisations.*
  - *A register should be established, or a formal systematic post market surveillance programme introduced when a new device is introduced so safety and efficacy can be judged when the device is used by the wider surgical community.*
  - *Surgeons should be reminded of the MHRA reporting system, particularly when a new device is introduced; a "red card" system should be seriously considered"*

  Since this, it remained an important goal for MHRA to gain a better understanding of the scale of the issue, including how many women were suffering adverse events relating to these devices, but also to better understand those who have benefitted from these procedures in treating incontinence and pelvic organ prolapse (which are a range of

conditions and can all be significantly debilitating due to a variety of causes but need to be considered independently and separately as the two conditions are quite different, each managed by several different procedures). We continue to raise awareness of reporting to MHRA as every report matters to us (see other responses for what we have done and continue to do).

See Annex D for adverse incidents reports we have received since 2010.

In general, the findings were then captured in the Department of Health led group in 2012 and the NHS England led Mesh Working Group in 2014 as detailed below who were responsible for taking forward the registry. This is being led by the Department of Health and Social Care and we are a member of their sub-group to help develop a registry.

More needs to be done by all those concerned to obtain better information and collect information over longer periods of time and that is why we have continued to support the implementation of a registry for procedures which use mesh and non-mesh to treat SUI and Pelvic Organ Prolapse (POP). See full response to Q11.

- **July:** At a Committee on Safety of Devices (CSD – Devices' independent expert committee) we raised awareness of March 2011 workshop as above and plans for information to be published. They agreed further investigation was required. See full response to Q36 for minutes of these meetings.

- **September:** Product specific information for vaginal tapes for SUI was published on the MHRA website to provide information to patients and healthcare professionals. This included a list of questions for patients to ask their surgeon prior to surgery. These are found in archived pages (because we moved to GOV.UK site in 2015).

  The number of adverse incidents reported was relatively small at that time (88 reports for SUI mesh tapes from 2005 - 2010) compared to the number of SUI mesh tapes manufacturers had told us had been sold in the UK (at least 46,000 for the same period). Through these pages and our relationship with the clinical community, we continued to highlight the need for informed consent between healthcare professionals and patients. This is on the understanding treatment offered is part of a recognised treatment pathway and in accordance with National Institute for Health and Care Excellence (NICE) Interventional Procedures Guidance (see below). Hence the publication of these pages to recognise the problem and give information that reflects the concerns of the public was essential. We also listed a number of questions for patients to discuss with their surgeon prior to surgery. This included:

  - Why have you chosen the use of surgical mesh or a traditional non-mesh repair in my particular case?
  - What are the alternatives?
  - What are the chances of success with the use of mesh versus use of other procedures such as traditional surgery?
  - What are the pros and cons of using mesh including associated side-effects and what are the pros and cons of alternative procedures such as traditional surgery?

  We let patient group representatives and the clinical groups/bodies know of these pages to raise awareness. To note, since late 2017, we have been working towards publishing a dedicated mesh page for the public and healthcare professionals to once again provide relevant and up to date information and to manage misinformation that can and has arisen around this safety concern. We anticipate this to be available late 2018. We will also provide adverse incident data similar to that found in Annex D. Meanwhile, we have

provided similar data to patients, media and healthcare organisations in response to questions they have raised.

- **September:** We wrote to all other EU Competent Authorities asking for information on numbers and types of failures within reports they had received on SUI tape and POP mesh. From the 9 countries who responded there was little evidence of problems or issues. No countries had identified any trend. We continued to keep this area under review as part of ongoing post-market surveillance.

2012

- **February:** We wrote to 4 mesh manufacturers who supplied to UK, for whom we had received most adverse events relating to their products, stating we were aware of concerns about vaginal mesh devices from women who have reported problems to us. We asked for information on: Clinical data and clinical evaluation report; details of their post market surveillance system and management review of data collected to date; UK/EU/Worldwide sales figures for last 10 years. We reviewed it and found no evidence that the information did not meet the relevant requirements within the Medical Device Directive when used correctly and it did not prompt regulatory action at that time. The decision to use mesh surgery for urinary incontinence and pelvic organ prolapse should be made between the patient and clinician, after discussing all the options and recognising the benefits and risks in the context of the distressing conditions being treated. We continued our market surveillance and engagement with a number of patient and clinical groups by taking the next steps.

  February/May: We appointed The University of York and York Health Economics Consortium to undertake a systematic review of the currently available literature of the incidence of frequently reported events (including postoperative pain, erosion and sexual dysfunction), associated with SUI and POP. Systematic reviews aim to find all the relevant evidence for a specific question, appraise its quality and provide a summary of the results. In May 2012, a further report was commissioned. See November 2012 entry.

- **March:** We met with representatives of "TVT-Messed up Mesh" group to listen to their concerns. They appeared to be a major support group for vaginal tapes and meshes at the time. The meeting was constructive, and they were reassured MHRA was taking their concerns seriously. A written response to the group afterwards said the issues they had raised about the devices and practices would be fed into MHRA's workshop with clinicians in March 2012 to discuss POP mesh, and that MHRA would keep them up to date with actions taken.

- **March:** We hosted a second workshop at MHRA but this time it was on POP mesh. Chaired by Prof Paul Abrams, attended by relevant leading expert clinicians in urogynaecology, including representatives of the Royal College of Obstetricians and Gynaecologists (RCOG), the British Association of Urological Surgeons (BAUS) and the British Association of Urogynaecologists (BSUG) together with representatives of the leading manufacturers of vaginal meshes to discuss device regulation, use and information for patients. Early draft findings from the PROSPECT trial were verbally presented to the group. Actions included:

  - List of responsibilities drafted for manufacturers, Notified Bodies, MHRA. Clinicians and hospitals (these were published here)
  - Discussion with Bruce Keogh about a register for these devices (taken up by Department of Health led group and subsequently the NHS Mesh Working Group)

- Writing to professional bodies about importance of reporting adverse events (facilitated by Committee of Safety of Devices (CSD) and our relationships with Royal Colleges etc)
- Request National Institute for Health and Care Excellence (NICE) to re-look at procedures associated with these devices (taken forward by NICE – see below)
- Patient information leaflets be developed by clinical community (see below)
- MHRA website pages updated to include notes of meeting and pages aimed at urology & gynaecology professionals (pages were published here),
- MHRA webpage aimed at patients (pages were published here),

- **March:** Ongoing communications with BAUS showed they proposed supporting a national audit relating to implanting of synthetic meshes for the management of incontinence. We actively supported this proposal promising input and support but saying we could not be a source of funds.

  As mentioned above in the 2011 entry, development of a registry is being led by DHSC who have subsequently secured funding for 3 years. This was announced on 21 February 2018 by the Secretary of State for Health and Social Care.

- **April:** We raised this issue at the Medical Devices Expert Group of all EU Competent Authorities stating that we suspected there may be more problems occurring with these devices than were currently being reported to us. After further subsequent meetings this eventually culminated in an EC taskforce set up to draft a remit for The Scientific Committee on Emerging and Newly Identified Risks (SCENIHR) to provide a scientific opinion on 'The Safety of surgical meshes used in urogynecological surgery' in 2013 (see Dec 2015 below). SCENIHR deals with questions relating to risks on broad, complex or multi-disciplinary issues requiring a comprehensive assessment of those risk.

- **April**: Minister Earl Howe was alerted to issues related to SUI tape and POP mesh in response to questions being raised in the media. Reference was made to two patient groups we were aware of. Due to increasing media interest, we kept the minister informed of the issues by providing further briefings in June and July plus responses to additional questions he raised.

- **July:** We met with representatives of Meshies United group to hear their concerns. We felt the meeting was constructive, and they were reassured that MHRA were taking their concerns seriously.

- **July:** Recommendations on how we communicate with the public on clinical issues was raised with CSD with particular reference to vaginal mesh. It was highlighted that there was a problem with the interface between device regulation, clinical guidance and professional performance. It was recognised MHRA had worked closely with the relevant Professional Bodies and Royal Colleges who were producing patient information leaflets and were working closely with NICE. Action Points were:
  - A bigger push was needed with the Speciality Societies and Royal Colleges encouraging them to report adverse events to MHRA
  - To consider issuing a Medical Device Alert. As described in response to Q10, Alerts are about raising awareness of a safety risk. So a decision was taken not to issue an alert as it was felt a precedent would be set with MHRA safety messages going beyond a safety message and amounting to giving clinical guidance, and that we would be crossing boundaries that were the remit of NICE – which NICE agreed.

- **July:** We contacted BSUG and BAUS several times about progress on patient leaflets, and for them to include a question 'what you should ask your surgeon before your operation'. BSUG patient information leaflets under development were available on their website for clinicians to modify as appropriate for their patients, however their website was not yet designed to be accessible to patients, although they were working on this. Clinical contacts informed us that Trusts do not generally allow clinicians to distribute patient information leaflets without going through their own vetting procedures.
- **August/September:** Brief overview sent to Minister Howe on progress with the 'York' report. With a further update sent in September with a draft copy of the report. Chief Medical Officer for England was also updated on progress of report.
- **September:** We chased clinical contacts for updates on patient information leaflets to either put on our website or provide a link to it. A number of bodies including RCOG, BAUS and BSUG subsequently published leaflets and were linked in the NHS E Working Group report, NHS Choices webpages, and on their own websites (updated over time).
- **October:** On behalf of DH, the NHS Medical Directorate organised Teleconference on Vaginal Tapes and Meshes. Chaired by Keith Willett (at that time Director, NHS Commission Board (NHS CB), attended by DH, MHRA, Director British Urological Institute; Vice-president RCOG and BAUS.

  The purpose was to review the current state of knowledge on the safety of procedures involving vaginal tapes and meshes, with particular reference to the pending publications of the York University review, and to consider what further action might be needed to improve the safety of the procedures, to reassure the public, and to manage the concerns of the patient advocacy groups.

  Possible further actions were minuted as:

  - Develop a proposal for a registry [BAUS & BSUG to lead as they had databases in use to collect data so the benefits and risks in clinical practice could be assessed]
  - Develop professional guidance for mesh [BAUS & BSUG lead]
  - Further promotion of good practice in informed patient consent [BAUS & BSUG lead]
  - Develop guidance for commissioners to encourage compliance with NICE guidance [DH/NHS CB lead]
  - Develop professional guidance on centres competent to carry out salvage surgery (BAUS & BSUG lead]

  Changes in DH meant this work was then handed over to its NHS Policy and Strategy Unit in April 2013
- **By November**: The March 2012 Workshop, made a number of recommendations on the responsibilities of parties involved in the manufacture, regulation and surgical provision of mesh and we published them on updated website pages for mesh for pelvic organ prolapse. The SUI web pages were also updated to include separate patient specific pages with suggested questions to ask their clinician as part of the informed consent process, links to NHS Choices, BAUS, BSUG and RCOG patient information and NICE guidance for patients. MHRA actively encouraged professional bodies BAUS and BSUG to develop patient information leaflets. These leaflets were subsequently published and were linked in the NHS E Working Group report, NHS Choices and on their own websites (updated over time).

Summaries of the Safety/Adverse Effects of Vaginal Tapes/Slings/Meshes for Stress Urinary Incontinence and Prolapse was published in November 2012 (York report). We also published this report on our website [archived pages] within our product specific information pages, where we gave a summary of their findings.

It is important to know several other reviews have taken place since this report, and many more papers have been published.

- **November:** A joint submission from the agency and the department went to the Minister asking for clearance on proposals for handling the publication of the York Report.

  Guidance and support for NHS surgeons on mesh implants was then issued and Sir Bruce Keogh wrote directly to NHS surgeons and Medical Directors to ensure they were aware of the guidance and findings of the York report and caution in interpreting those findings on adverse event rates. It should be noted several other reviews have taken place since and many more papers have been published.

  CSD were made aware of the York report and the NHS guidance mentioned in the above See full response to Q36.

  We continued to keep this area under review as part of ongoing market surveillance.

2013

- **June:** No further action had been taken since the DH teleconference in October 2012 due to major organisational changes in DH and the dissolving of the DH NHS Medical Directorate. MHRA prompted scheduling of regular meetings with the newly formed NHS Commissioning Board, and DH Policy to push forward the actions from the October 2012 teleconference.
- **September:** Lord Howe, Catherine Calderwood (National Clinical Director for Maternity and Women's Health) and John Wilkinson (Devices Director) met with representatives of patient group "Meshies United". These meetings were followed up by a written response from MHRA to the patients addressing the questions they had raised.
- **December:** MHRA contributed to an NHS England letter sent from Prof Bruce Keogh to Area Team and Regional Medical Directors on 'The Surgical management of urinary incontinence and pelvic organ prolapse' and was co-authored and supported by Dr Catherine Calderwood, National Clinical Director, Maternity and Women's Health, NHS England; RCOG; BSUG; and BAUS. It was aimed at all practitioners involved in the surgical management of SUI and POP particularly in regard to the use of surgical mesh. It advised that investigation and management of all such patients should follow NICE guidance. Of particular relevance the important issues highlighted were: patient consent; regular audit as recommended by NICE; reporting adverse incidents involving mesh to MHRA; surgery for mesh removal to be performed by specialist commissioned services.
- **December:** MHRA wrote to 7 mesh manufacturers known to supply the UK, as part of our on-going market surveillance of devices asking for up-to-date information on:
  - Outcomes of any post-market clinical follow-up undertaken
  - Summary of post market surveillance (PMS) activities
  - Most recent analysis of this PMS activity
  - Most up to date risk assessment for their mesh devices
  - Had they considered HES statistics on the number of operations associated with the removal of these implants; and information from the York report published in November 2012.

In common with other medical device regulators worldwide, none of whom had removed these devices from the market, we were not aware of a robust body of evidence which would lead to the conclusion these devices were unsafe if used as intended in an appropriate treatment pathway where the associated benefits and risk have been considered during the informed consent process. We continued to keep this area under review as part of our ongoing market surveillance.

2014

- **June:** The Chief Medical Officer for England requested we produced a report to advise on whether from a regulatory perspective, the benefit and risk assessment remains correct of vaginal mesh implants. A report titled; 'A summary of the evidence on the benefits and risks of vaginal mesh implants' was published in November 2014.

  It was found there was no justification for the Agency to undertake any additional regulatory action at this time, based on the extensive findings and research undertaken during the production of this report. MHRA's position at that time was that for the majority of women, the use of vaginal mesh implants was safe and effective. However, as with all surgery, there is an element of risk to the individual patient. This conclusion is entirely dependent on compliance with the National Institute for Health and Care Excellence (NICE as mentioned in 2013 December entry) and other sources of guidance which emphasise the caution that should be exercised prior to surgery being considered. Whilst some women have experienced distressing and severe effects, the current evidence shows that when these products are used correctly they can help alleviate the very distressing symptoms of SUI and POP and as such the benefits outweigh the risks.

  However, we did acknowledge that:

  - benefit is difficult to quantify, and
  - the decision of what is an acceptable risk in any given condition with respect to any individual patient ultimately rests with the clinician and patient and is at the heart of the informed consent process

  We did conclude further work needs to be done to characterise long-term safety in relation to different surgical procedures and vaginal mesh implant types – subsequently taken up by NHS England Mesh Working Group and now by DHSC (to develop a registry as its within their remit).

  Since this report, the key points in its 'Next steps' section (page 88) have been addressed.

  This report was commented on by the following external organisations: NICE, RCOG, BSUG and BAUS, and our Committee on the Safety of Devices and Register of Experts, who were all supportive of the report.

- **June:** After extensive meetings and preparatory work between MHRA, NHS England and Department of Health (DH); the NHS England led Mesh Working Group was formed to better understand the issues and what should be done to tackle them. Membership was drawn from DH, NHS England; Scottish Government; professional societies (British Society of Urogynaecology (BSUG), British Association of Urological Surgeons (BAUS) and the Royal Colleges of Obstetricians and Gynaecologists (RCOG)), MHRA, along with patient interest groups. Wales and Northern Ireland Governments were to be kept informed.

- **2014**: A Scottish Independent Review group of the use, safety and efficacy of transvaginal mesh implants in the treatment of stress urinary incontinence (SUI) and pelvic organ prolapse (POP) was formed and MHRA provided input. See 2015 and 2017 entry below for interim and final report.
- **2014 onwards:** MHRA has been a participant and contributor to the National Institute for Health and Care Excellence (NICE) Interventional procedure guidance (IPG) programme relating to mesh as a committee member of the Interventional Procedures Advisory Committee (IPAC). NICE has published up to date guidance on interventional procedures relating to mesh used in the treatment of POP or SUI (see November 2017 below).
- **December:** We emailed the 6 main mesh manufacturers known to supply the UK asking for a copy of their 'biological safety assessment' for their vaginal mesh implant devices. The information we received contributed to the MHRA peer reviewed paper published in June 2016 (see below).

2015

- October 2015: Scottish Independent Review published its Interim Report ' The Scottish Independent Review of the Use, Safety and Efficacy of Transvaginal Mesh Implants in the Treatment of Stress Urinary Incontinence and Pelvic Organ Prolapse in Women'. It considered published evidence, patient stories and the opinion of clinical experts. In addition, an epidemiological study has been conducted using routinely reported Scottish hospital inpatient data. It made 8 conclusions, which included informed consent, training and clinical governance.
- **November:** Devices Expert Advisory Committee (DEAC) discussed mesh. See full response to Q36.
- **December:** We and other EU Competent Authorities (in 2013) had input into a drafting a scope/mandate of an eventual SCENIHR mandate. An EU Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) published its 'Final Opinion on The safety of surgical meshes used in urogynecological surgery' and we noted it broadly echoed some of findings of the Scottish Initial Review and English Working Group interim Report. It stated:

  - Material properties, product design, overall mesh size, route of implantation, patient characteristics, associated procedures (e.g. hysterectomy) and surgeon's experience are aspects influencing the clinical outcome following mesh implantation. Such aspects are to be considered when choosing appropriate therapy.

  - For all procedures, the amount of mesh should be limited where possible.

  - The implantation of any mesh for the treatment of pelvic organ prolapse via the vaginal route should be only considered in complex cases in particular after failed primary repair surgery.

  - A certification system for surgeons should be introduced based on existing international guidelines and established in cooperation with the relevant European Surgical Association.

  - Appropriate patient selection and counselling, which is of paramount importance for the optimal outcome for all surgical procedures, particularly for the indications discussed. This should be based on the results of further clinical evidence, which should be collected in a systematic fashion for all of these devices.

In general, the above was captured in the NHS Mesh Working Group and/or Scottish Review.

- **December 2015:** NHS England Mesh Working Group Interim Report was published and our response to it is here. It was again recognised that a better understanding of the true nature and extent of the complications with these devices needed to be established. There were recommendations for MHRA to continue to raise awareness amongst clinicians and patients to report events to us any time (retrospectively) and to ensure women are aware that patient identifying details will only be passed on to the manufacture if they give permission. See 2017 entry for update on our progress to meet recommendations within our remit. Regarding establishing a registry, recommendation 4 says:

I&DREC4	**A cost/benefit analysis of establishing a registry for these procedures should be undertaken at the earliest opportunity.** *Rationale for recommendation:* As set out in the rationale for I&DREC3, it is very difficult to ascertain the true rate of adverse incidents for these procedures. Ideally, the group would like to see the establishment of a registry to provide this as well as data on the longer term outcomes of these procedures. The registry would need to differentiate between products. However, recognising the financial implications of establishing such a registry, a cost/benefit analysis should be undertaken in the first instance to inform discussions on whether such a registry would be viable and the scope for using and building on existing data sources.	NHS England Department of Health (DH)	Agreed

For several years, we have been active participants in the DH/DHSC and NHS E led sub-working groups to drive forward the development of a registry (see 2011 section for our original call for a registry). Even though developing a registry does not come under our remit, we remain committed to providing regulatory input (see below for progress by DHSC) and have since attended a number of DHSC meetings with professional bodies such as BAUS and BSUG and representatives from the Devolved Administrations.

2016

- **February:** Devices Expert Advisory Committee (DEAC) discussed mesh. See response to Q36.
- **June**: A peer reviewed paper was accepted for publication in the International Urogynaecology Journal titled “In vivo response to polypropylene following implantation in animal models: a review of biocompatibility”. The evidence shows polypropylene evokes a less inflammatory or similar host response when compared with other materials used in mesh devices.
- **June:** Devices Expert Advisory Committee (DEAC) discussed mesh. See response to Q36.

2017

- **March:** Scottish Independent review published their final report. We noted the update, conclusions and recommendations made and that the report found mesh procedures for both stress urinary incontinence (SUI) and pelvic organ prolapse (POP) carry a risk of complications which, in some cases, are life changing and cannot be corrected. However, for the majority of patients, such serious complications do not occur. Also noted was mesh must not be offered routinely to women with pelvic organ prolapse, and the importance of informed consent.

The Scottish Government requested that Health Boards suspend mesh procedures (except in limited circumstances where women had distressing symptoms and gave fully informed consent to proceed). The request for suspension remained in place until the Chief Medical Officer is satisfied that the recommendations of the review have been implemented. This instruction has been superseded by the halt on use of certain mesh procedures in Scotland. See 2018 entry.

25 October 2018 'An Investigative Review into the process of establishing, managing and supporting Independent Reviews in Scotland' chaired by Professor Britton was published. We are aware of the number of criticisms on how the mesh review for the 2017 report was conducted. However, we noted in the Review:

"*The task of this investigation has not been to reconsider the merits of the Mesh Review's substantive conclusions on the safety and efficacy of transvaginal mesh implants, nor have we sought to apportion individual blame for any failing or omissions. That was not our remit. We have however, attempted to discover what caused the Mesh Review to be received in the way that it was."*

We understand the 2017 Report's conclusions and recommendations still stand at this time. We will consider if any lessons can be learned from the Scottish Review to drive our own improvements.

- **July**: The final NHS England's Mesh Oversight Group Report was published which aimed to address the 3 major concerns expressed by the patient interest groups – they were clinical quality, data collection and information and informed consent. The report did not recommend banning or suspending the use of mesh. The report showed we had made progress, at that time, to address the recommendations in our remit (REC 3) to improve adverse event reporting associated with use of mesh via our Yellow Card Scheme.

  Outputs from the above Report and Review include but not isolated to:

  - Two comprehensive patient information leaflets have now been produced in collaboration with the Scottish Independent Review of Transvaginal Mesh Implants Working Group for Scotland. These leaflets contain links to our Yellow Card Scheme to report adverse incidents involving medical devices.

  - The Royal College of Obstetricians and Gynaecologists (RCOG) will promote these resources to women and the public via the 'Patients' section of its website and via its Women's Network and Women's Voices Involvement Panel.

  The Report also showed progress by the NHS to provide more consistent information to patients, GPs and surgeons, including a checklist to be signed by both the patient and surgeon to ensure the patient had read and understood all of the information associated with the use of mesh.

  With regard to the recommendation to develop a registry which came under DHSC and NHS responsibility, it reported that

  '*The registries sub group continues to work to develop a way of allowing the tracking of the mesh device that women receive. The aim is to gain a complete picture of complications and when they occur. The group is examining options to see if there is now a straightforward solution that uses new technology and ways of gathering information. The group is looking at the potential of existing databases…'*

  See 2018 ongoing work entry for DHSC workshops to move this forward.

  Various clinical, patient groups and professional bodies have information on their websites about reporting adverse incidents to us. For example:

The British Association of Urological Surgeons (BAUS) and British Society of Urogynaecology (BSUG) has a webpage dedicated to MHRA and an explanatory guide to reporting adverse incidents.

Various patient groups relating to mesh implants have information on their website about reporting adverse incidents to MHRA. For example, the Scottish Mesh Survivors group has on its website very positive and useful information about adverse incident reporting via the Yellow Card.

- **November**: Therapeutics Goods Agency (TGA regulator in Australia) announced the removal of all transvaginal mesh products whose sole use is the treatment of pelvic organ prolapse (POP) via transvaginal implantation and all single incision mini-slings for the treatment of stress urinary incontinence (SUI) from its register; effectively ceasing legal supply of these devices. No other mesh devices for the treatment of POP or SUI are affected and so remain on the registry and can be used.

  New Zealand authority MEDSAFE followed the same action as TGA in January 2018. However, individuals are still able to purchase these devices from overseas if there is a clinical need.

  The evidence, reviewed by the TGA, which includes information from the manufacturer and published/scientific studies is not new or is information regarding the device safety we have not already considered. Some of the evidence, particularly review of the literature has also been considered by NICE, the Scottish Independent Review and NHS E Mesh Report.

  We compared this with NICE Interventional Procedures Guidance for the procedures which use a transvaginal approach; none recommended 'do not use' (see Annex E). They did recommend special arrangements for clinical governance, consent and audit in all the cases, except guidance for transvaginal mesh repair of anterior or posterior vaginal wall prolapse which stated:

  "there are serious but well-recognised safety concerns. Evidence of long-term efficacy is inadequate in quality and quantity. Therefore, this procedure should only be used in the context of research".

  This does not constitute a "back door ban", but shows the procedures have a clinical place and need a greater body of evidence in the longer term to better understand efficacy and safety. The recommendations are generally consistent with the Scottish Review (noting the noting the recently published Investigative Review by Professor Britton) and NHS England Oversight Group Report recommendation that vaginal mesh should not be routinely offered as the first surgical intervention when treating prolapse.

  NICE's decision to change its recommendation on single-incision short sling mesh insertion for stress urinary incontinence in women from "research only" to "special arrangements" was, because in their view the procedure was no longer considered new and the level of uncertainty regarding efficacy and safety was deemed to no longer require scrutiny from a research ethics committee.

  It is important to note that, in Australia there are no independently published clinical guidelines for these procedures because Australia does not have an organisation with the capability to conduct the detailed work NICE undertakes.

  MHRA and all other EU Members States including a small number of international regulators acknowledged the actions taken by TGA. MHRA decision not to take regulatory action has been based on the continued availability of mesh in the UK being underpinned by evidence that the devices have conformed to the requirements of the current legislation in the EU. In doing so they are deemed acceptable safe when used as

intended, with the understanding no medical procedure, medicine or medical device is without risk. It includes use within appropriate treatment pathways, which are determined by healthcare institutions and healthcare professionals. This is also supported by the fact that based on current evidence, no other regulator in Europe, USA or Canada has taken regulatory action to restrict or stop use of mesh (only Australia and New Zealand has at the time of writing this response.

Like us, they have and continue to keep the evidence under review.

- Again, as part of ongoing post market surveillance, we decided that UK manufacturers needed to be contacted for their post market data, a copy of the instructions for use and their plan for any updates/action in light of the NHS England working party report, NICE IPGs and TGA and MEDSAFE action. The work is ongoing and is in collaboration with a number of other EU Competent Authorities. This is broadly speaking a repeat of our post market surveillance of a number of manufacturers of mesh in 2010, 2012 and 2013 and within the report commissioned by the CMO detailed above. A letter to manufacturers was sent requesting information including their clinical evaluation report, the latest risk benefit analysis, a summary of post market data, a copy of the Instructions for Use and details of any action following the recent publications and updated guidance from NICE.
- **December:** MHRA presented at the monthly EU vigilance teleconference of EU Member States (see device response to Q5) to advise them of our intention to contact manufacturers, ask if other member states had similar concerns and are any further actions being taken, and should there be an EU Taskforce or separate teleconference to discuss the ramifications of the decision taken by TGA. As a result, a follow up teleconference with interested member states (Surgical Mesh Taskforce) was held and it was agreed coordination with member states is beneficial and comments were received on the letter to manufacturers.
- Information from many sources including, our own report for the CMO in 2014, a Cochrane review, and recent papers such as Morling, Nature, JAMA and subsequently the NHS Digital Review (see 2018 below) with thousands of patients being studied and hundreds of studies reviewed both in the UK and beyond. Many of these publications including the studies looked at as part of the NHS England Report and Scottish Review indicate there are very large numbers of women who are helped by surgery using these devices and there is a place for them in appropriate treatment pathways. When to use mesh surgery for urinary incontinence and pelvic organ prolapse should be made between the patient and clinician, after discussing all the options and recognising the benefits and risks in the context of the distressing conditions being treated.

  While complication rates only form part of the picture, they have been a prominent part of the wider public debate. The rates will vary based on which source is examined. As always, these figures need to be interpreted with caution, consideration must be given to the individual procedures being undertaken, skill of the surgeon, the temporal relation to the procedure, the severity of the complication and what actions if any were required to address the complication.

  Complication rates can inform clinical and regulatory decisions, but they have to be contextualised to be useful.
- Throughout the latter part of 2017 and into 2018, we provided responses and briefings to DHSC, our Minister; Lord O'Shaughnessy, the Secretary for State for Health and Social Care; Rt Hon Jeremy Hunt, Members of Parliament (including All Party Parliamentary Group on Surgical Mesh Implants, (APPG) and Chief Medical Officers across the UK

outlining what we have and continue to do to address the concerns of patients and protect public health.

2018

- **February:** A second EU Surgical Mesh Task Force teleconference was held. It was suggested that the lead Competent Authority would review the information from manufacturer and there was a discussion how to review the manufacturer information with a systematic approach and the priority for different devices. It was agreed POP would have priority and that UK would draft a methodology. This project planning work continued over the next few months – seeking input from other Competent Authorities and coming together to agree a way forward.
- **February**: Devices Expert Advisory Committee (DEAC) discussed mesh. See full response to Q36.
- **April:** Following a feasibility study developed by MHRA and NHS England that was sent to Lord O'Shaughnessy to consider to take forward, NHS Digital then published a Retrospective Review of Surgery for Urogynaecological Prolapse and Stress Urinary Incontinence using Tape or Mesh: Hospital Episode Statistics (HES), Experimental Statistics, April 2008 - March 2017 to gain a clearer picture of patients who have has such procedures.

  This was followed an independent commentary by Policy Innovation Research Unit (PIRU), both identifying the statistics are classified as experimental and should be used with caution. Its overall conclusion was:

  "*the NHS Digital Review findings are consistent with many studies (both randomised controlled trials and observational studies) in confirming that some women will experience adverse effects of mesh and tape implants to the extent that removal is necessary. The scale of any problems cannot be accurately determined."*

  We then responded to Dame Sally Davies (Chief Medical Officer for England) request for our initial views of this data which said:

  "Despite the known limitations of these data, detailed below, it generally shows the rate of reoperations to be in the range 0.1 – 1 percent. This is similar or lower than figures detailed in other recent studies. However, these are not a rate of complications (reoperations do not necessarily mean complications) and other studies have also considered other end points which have different strengths and weaknesses in attempting to determine what complications occur and how frequently. All these studies show that most of these operations are not followed by reoperations or complications beyond the usual issues of recovering from surgery. (e.g., pain, discomfort, initial urinary retention).

  The review, when added to the large body of evidence we have considered over many years (including individual adverse event reports, published studies, reports and reviews), does not justify grounds for taking regulatory action. We, and other European regulatory authorities, continue to allow the use of surgical mesh to treat the debilitating conditions of incontinence and organ prolapse when used in an appropriate treatment pathway, where the associated benefits and risk have been considered during the informed consent process."

  We understand other organisations were contacted for their views also.

- **May:** A third EU Surgical Mesh Task force meeting was held to confirm which other EU regulators were to review information, review the methodology and develop a project plan. As a result, a small working group was set up consisting of five regulators including

MHRA. Over the next few months, a great deal of work carried on to agree a methodology.

- **June:** Devices Expert Advisory Committee (DEAC) discussed mesh. See full response to Q36 (note, minutes are to be formally agreed in November's DEAC scheduled meeting).
- **July:** Following a recommendation by the Independent Medicines and Medical Devices Safety Review, the government and NHS paused the use of vaginally inserted surgical mesh for stress urinary incontinence until a set of conditions to ensure that patients receive safe and high-quality care are met. This pause was extended to include vaginally inserted surgical mesh for pelvic organ prolapse and will be implemented through a high vigilance scrutiny programme of restricted practice. The pause is broadly similar in Northern Ireland and Wales.

  In response to this we published a statement on our website which stated:

  "There has not been any new evidence which would prompt regulatory action and the position of MHRA remains the same on these medical devices. We continue to work with other regulators in the EU and wider, as well as colleagues across the health sector, to monitor and examine evidence as it becomes available."

  We continue to work with DHSC to support the delivery of the pause conditions as appropriate.

  12 September 2018 the Scottish government announced a halt in the use of tapes for the treatment of stress urinary incontinence and mesh for pelvic organ prolapse. A restricted use protocol and high vigilance scrutiny has been introduced. It is expected no further patients will have surgery involving use of this type of mesh until the halt is lifted.
- MHRA met with representatives of Mesh UK Charitable Trust to discuss concerns and what we were doing to address those concerns. We provided two written responses providing relevant information.
- **July/September:** As part of the ongoing post market surveillance role of MHRA and other EU regulators, the assessment of certain information from manufacturers started. Its aims are to establish whether the instructions contain suitable warnings, clinical evaluation report is adequate, the benefit-risk analysis is adequate and up to date. Any issues found will be sent to the manufacturer, notified body and the relevant EU competent authority (who is responsible for the designation of the notified body), who will monitor any corrective actions that are required and that they are done as quickly as possible. We are closely monitoring these actions, so they are done as soon as possible.

  The EU monthly vigilance teleconference was updated on this point and we continue to collaborate with other EU competent authorities and share information.

  An Expert Advisory Group (EAG) for urogynaecolgoical procedures is meeting in November. It is anticipated they will specifically advise on the outcomes of this post market assessment of mesh when available.

2018 Ongoing work:

- We continue to raise awareness of the need to report adverse incidents related to these medical devices. Some professional bodies and patient groups have links to our Yellow Card Scheme to report adverse incidents to MHRA. This also includes NHS Choices and the NICE IPG documents for use of mesh. We have seen an increase in reporting by the public/patients and healthcare professionals (see Annex D for adverse event information). There is no time or entry limit for an incident to be reported so anyone who may have long term complications can also report to MHRA.

- We continue to respond to women, patients, members of the public and the media to respond to their written questions and concerns, and to outline what we have done and doing to continue to protect public health. We have also listened to several women who have called us to share their experiences and concerns and we have obtained information to formally log their report on our system for further investigation. All reports are acknowledged by us.
- MHRA continues to monitor adverse events related to all surgical meshes and is strongly encourages reporting. The reports received reflect both minor and major known and well documented complications (found in the manufacturer's instructions for use), as well as those temporally related to the procedure and others, which have occurred over time. It should be stressed these reports do not reflect actual complication rates for the various procedures, of which there are a number, each with its own complication rates.
- The main reported complication following urogynaecological procedures is post-operative pain, which may be temporary, but may become a chronic complication and this can occur even in the absence of a repair using a synthetic implant. This type of pain may be very debilitating and extremely difficult to treat in some patients.
- Other complications related to surgery for urogynaecological procedures in the peri-operative period include, erosion (migrated, or become partially exposed through vaginal tissue), infection, bleeding, organ perforation/fistula formation, ureteric injury, wound dehiscence, vessel or nerve injury and urinary retention. A later complication, which causes much understandable distress, dyspareunia is also reported.

  These must be balanced against the fact they occur in a minority of cases and the serious conditions they are treating, such as urinary and faecal incontinence, external prolapse of pelvic organs including the vagina, cervix and rectum.

  It is important to know that no procedure is risk free (including where mesh is not used).
- Since 2010, we have generally seen an increase in reporting by members of the public, patients and healthcare professionals for mesh used to treat SUI and POP. We have also seen an increase of reports where they do not know or include at the time of reporting, what mesh they have implanted for us to determine if it has been used in the treatment of SUI or POP (hence 'unknown indication of use'). See Annex D for adverse incident information. In the summer of 2018, we made a small change to Yellow Card, so the public are asked what the device is used for (if they know). We feel this will reduce the number of 'unknowns' reported to MHRA and help with our analysis of the data.

  We have built relationships with the clinical community including the Royal Colleges and NICE to share experiences and promote reporting to us (recommendation 1 and 7 of the Stephenson Report – see 'Expert clinical advice – MHRA medical devices independent review: report on progress' in response to Q9).

  We are in the process of contacting the clinical community to ask them to continue to report to us via Yellow Card, even retrospectively.

  Dr Ian Hudson; Chief Executive of MHRA and Professor Sir Michael Rawlins; Chairman of MHRA have met with a number of professional and clinical bodies to promote reporting to MHRA (see response to Q3).
- We are currently gaining an understanding of the value of CPRD data for supporting medical device market surveillance (vigilance). Clinical Practice Research Datalink (CPRD) linked data is anonymised primary care patient data that can be individually linked to secondary care and other health and area-based datasets. This linkage enables CPRD to provide a fuller picture of the patient care record to support vital public health research, informing advances in patient safety and delivery of care.

CPRD is jointly sponsored by us and the National Institute for Health Research (NIHR), as part of the Department of Health and Social Care.

We have started an exploratory epidemiology study and further details of this case study can be found in the study protocol (a summary of which will be published here on or about 02 November 2018) which has been approved by the CPRD Independent Scientific Advisory Committee (ISAC). The overall aim of the study is to assess the value of linked CPRD data to support MHRA's medical devices vigilance processes within a regulatory context. The study will take a descriptive exploratory approach and will explore the incidence of different events in a cohort of women who have undergone a procedure for stress urinary incontinence or pelvic organ prolapse in England.

An assessment of the data will be undertaken at each stage of the analysis before we draw any conclusions as this is the first time routine primary care data has been explored for medical device surveillance within the Agency. This type of information can help us to understand if CPRD data can help contribute to MHRA devices vigilance practices or help us to refine risk minimisation measures or regulatory advice. So, the focus is on understanding the value of CRPD data for supporting device vigilance rather than mesh per se

- MHRA has provided input into Scan4Safety and unique device identifiers (UDI) long term initiatives to track devices in individual patients over a longer period of time to gain a more complete picture of complications and when they occur and thereby considerably improve future patient safety monitoring. See full response to Q31.

  The MHRA recognises the value of collecting Unique Device Identifiers (UDI) for implantable medical devices in patient electronic records in support of device post-market surveillance and patient tracking and tracing. This has also been recognised in the Government's response to Sir Bruce Keogh's Review of the Regulation of Cosmetic Interventions (13 February 2014), which states

  "NHS England and Trusts will encourage surgeons and nurses to adopt good practice in recording and reporting use of devices to implement registries and roll-out of UDI"

  and in the NHS eProcurement Strategy (7 May 2014) which states

  "*Once providers of NHS services have implemented GS1 coded patient identification, they should seek to integrate the recording of the use of medicines and implantable medical devices into patient records by means of scanning the patient identity wristband and the unique device identification barcode(s) on the product".*

- MHRA continues to work with and support NHS England and the Devolved Administrations in implementing the recommendations of the Scottish and English reviews on matters within its remit, to further increase patient safety and public health.
- We continue to hold conference calls with DHSC, NHS England and NICE to discuss mesh and share information where appropriate.
- We continue to be active members of the DHSC led group to develop a registry. DHSC have recently commissioned Healthcare Quality Improvement Partnership (HQIP) to run workshops in November for all those involved including patients to discuss its development, including a look at existing databases run by BAUS, BSUG and The Pelvic Floor Society. We will be attending to provide input and drive forward best practice for registry development (also see response to Q11).
- MHRA has been instrumental in agreeing new EU regulations to strengthen the regulatory framework. They came into force in May 2017. One of the most important changes introduced is to significantly increase the requirements for robust pre-market clinical data – particularly for implantable devices – and ensure that manufacturers are

meaningfully following their devices in the clinical setting once they have received regulatory approval.

- We were made aware of repeated calls by Members of Parliament for these devices to be reclassified as “high risk”. Under the current EU Medical Device Directives (published in 2007), most of these medical devices are already classified as medium to high risk as Class IIb medical devices, some containing biological material are classified higher at Class III. This classification system reflects the appropriate conformity assessment route to be taken to obtain a CE mark and both require an assessment by a Notified Body.

  The new EU Medical Device Regulations already includes a change to the classification so all “surgical mesh” devices intended for “long term or permanent use” will become Class III. This change does not change the standards that the device must meet, or the level of clinical evidence required but will mean a greater level of scrutiny on the device in both pre- and post-market assessments (see full response to Q33).

- MHRA, from its involvement in the reviews and reports undertaken, and its work with NICE feels it is clear there remains a clinical need for these devices in appropriate treatment pathways, which have been considered in detail by clinicians and the professional bodies who represent them.

  We, and other European regulatory authorities, continue to allow the use of surgical mesh to treat the debilitating conditions of incontinence and organ prolapse when used in an appropriate treatment pathway, where the associated benefits and risks have been considered during the informed consent process.

  We continue to support NHS England in meeting the IMMDSR pause conditions within our remit.

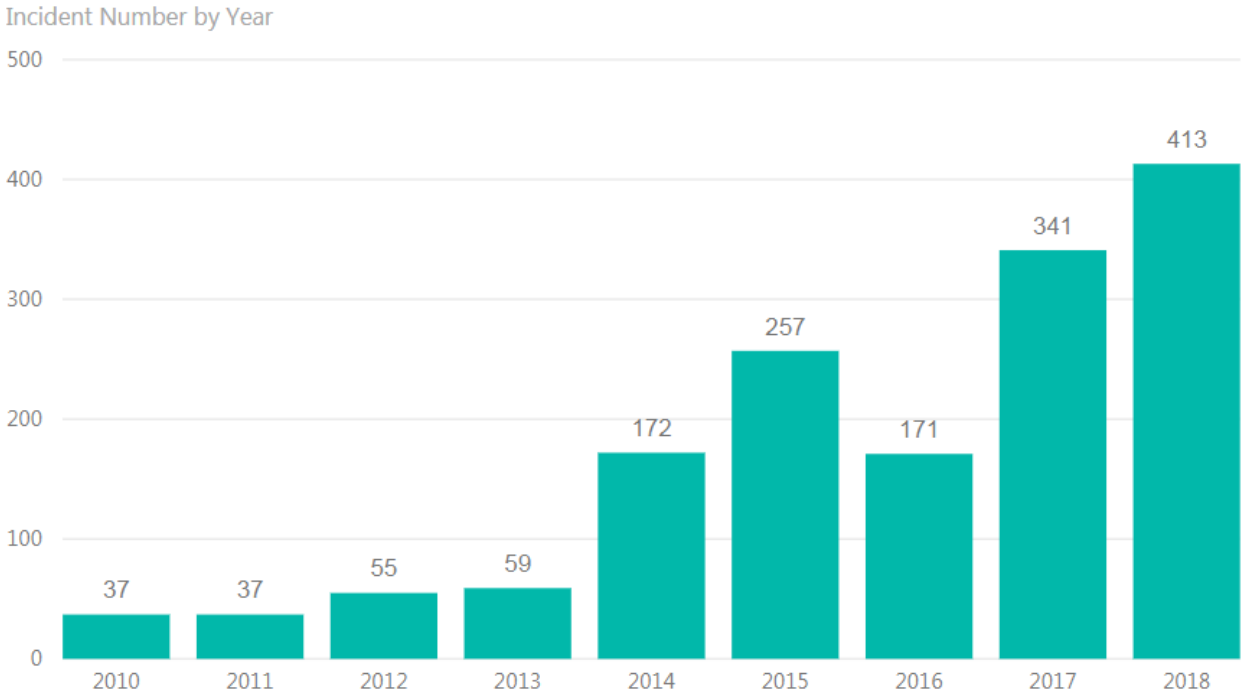
  We recognise the publication of more data/information on the safety of medical devices is an on-going process, occurring as more experience is gained into the use and complications associated with any clinical procedures, including those using urogynaecological devices. We have and will continue to keep the evidence under review. We will act as necessary to continue to protect the health of all patients who need treatment.

Annex D: Abdominal and Vaginal Pelvic Mesh Adverse Incident Figures for Q1

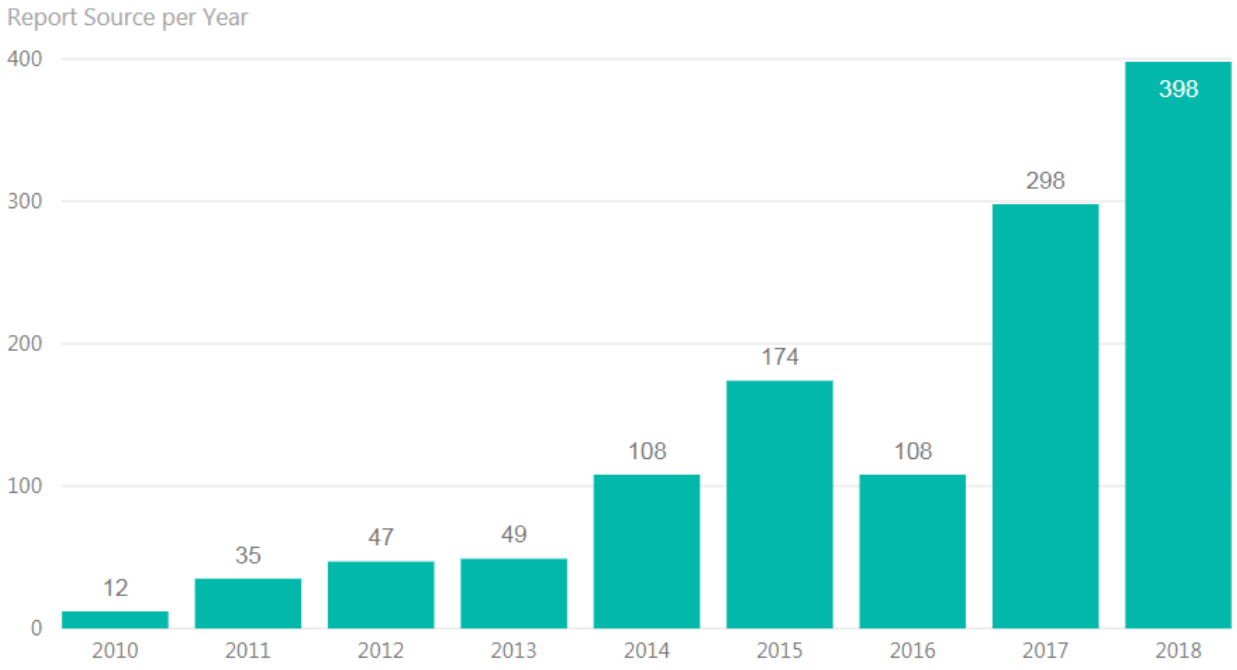
*See notes below associated with these data

1. Surgical Mesh incidents for Stress Urinary Incontinence (SUI)

All adverse incident reports (AIRs) – From Manufacturer, Healthcare Professional and Member of Public

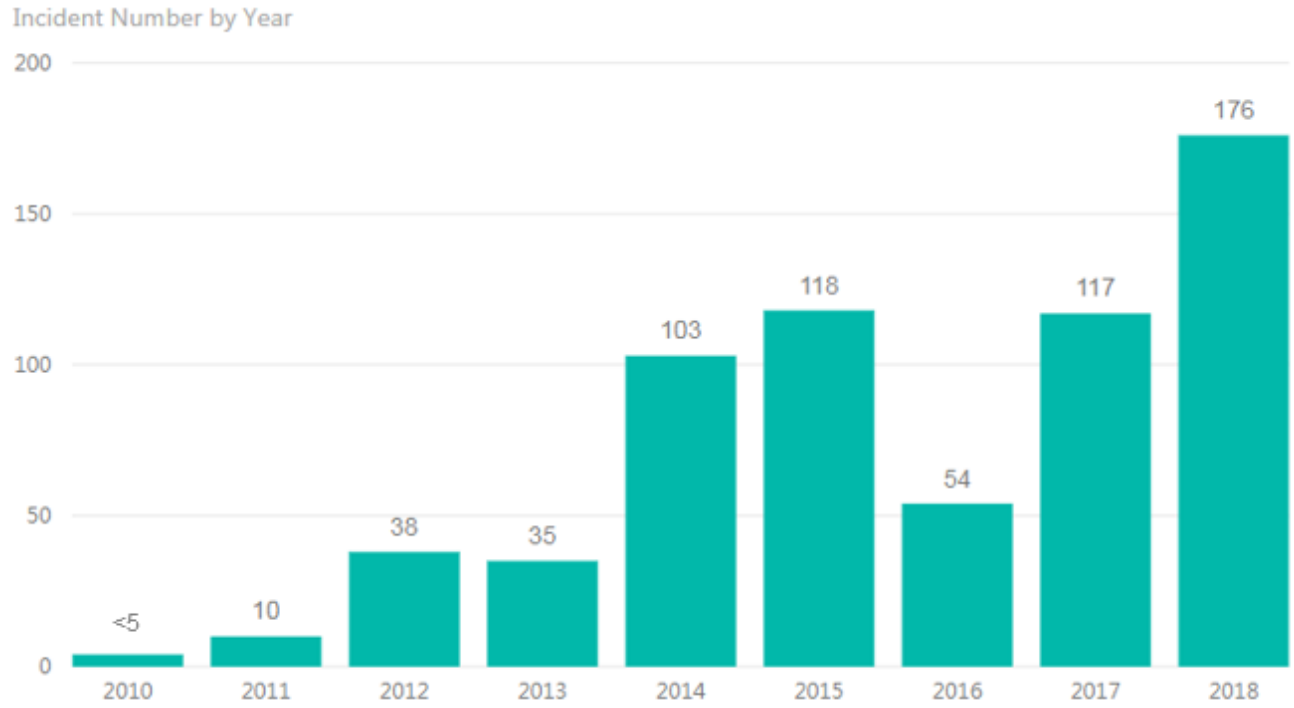


Healthcare professional and Member of Public reports only

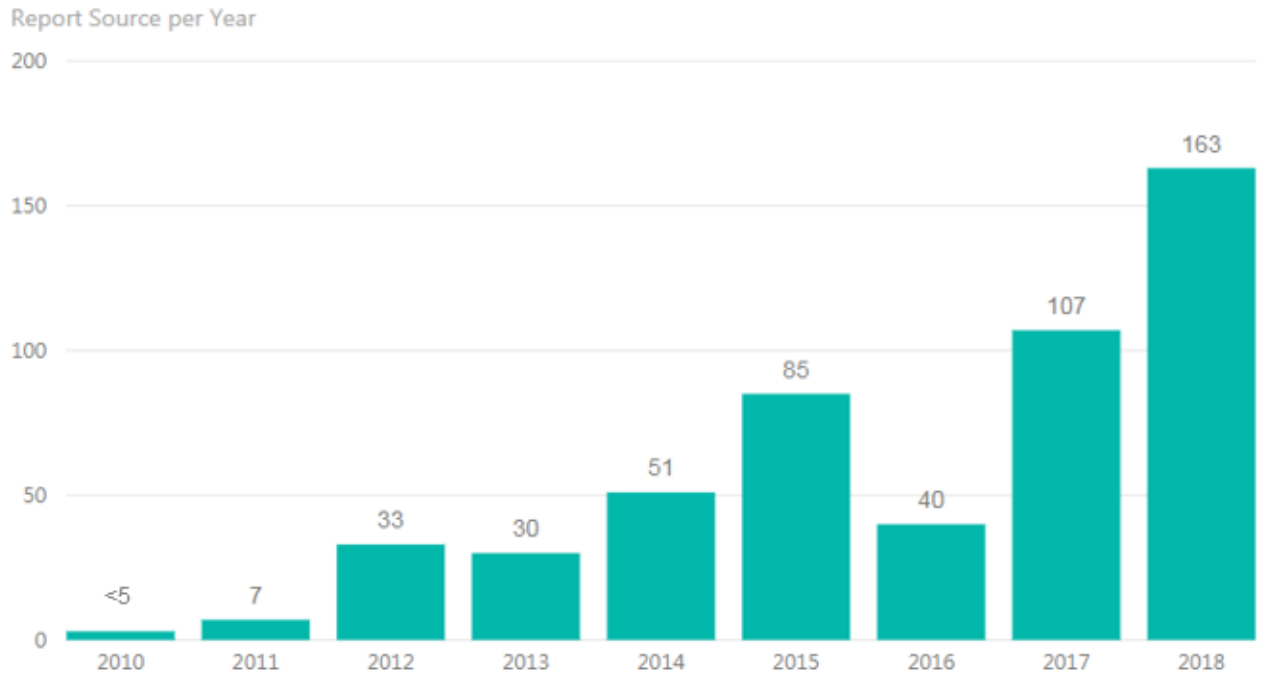


2. Surgical Mesh incidents for Pelvic Organ Prolapse (POP)

All adverse incident reports (AIRs) – From Manufacturer, Healthcare Professional and Member of Public



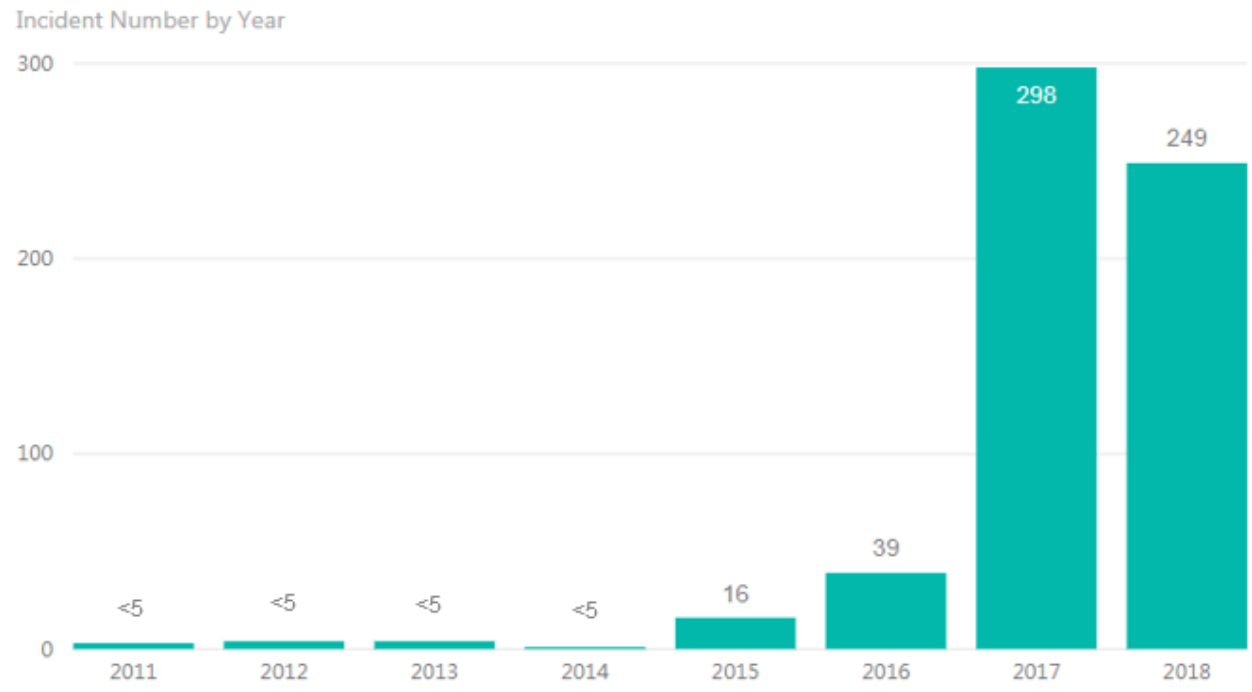
Healthcare professional and Member of Public reports only



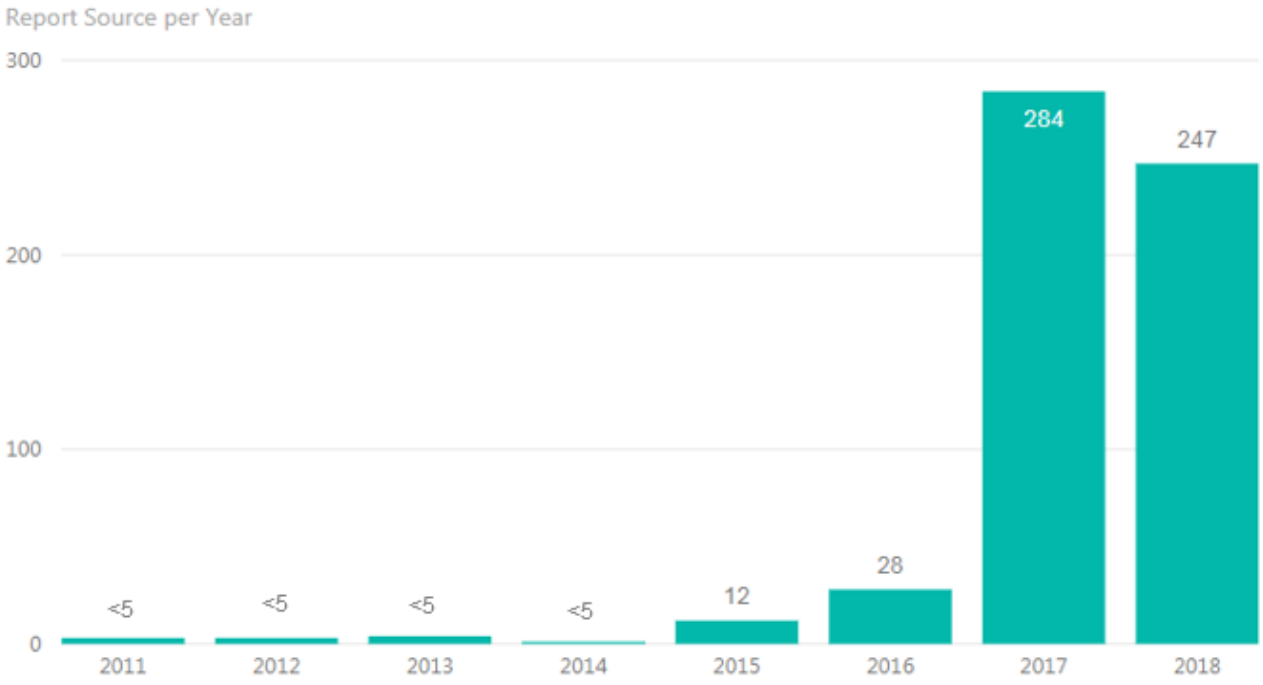
3. Surgical Mesh incidents for Unknown Indication

All adverse incident reports (AIRs) – From Manufacturer, Healthcare Professional and Member of Public

Note: There are no incidents logged on our database for 2010 for Unknown Indication



Healthcare professional and Member of Public reports only



*Please note:

- These numbers are accurate at the time we extract them from our database. Minor changes in the numbers can occur if more details are provided at a later date, such as a change to the indication of use.
- These figures are not the same as complications rates
- It should be noted that this information may include a range of recognised complications related to this type of surgical procedure and do not necessarily indicate a fault with any particular device.
- As with any medical device, their use carries the risk of complications and they occur with all types of surgery varying with time and anatomical location. The spectrum of complications is well known for these procedures and the nature and severity depend on a number of factors. These include the pre-existing health of the patients, the complexity of the medical condition being treated, the surgery being undertaken, the skill of the surgeon and in surgery using medical devices; the particular device being used and the healthcare system in general. The majority of the conditions being treated with these devices are highly complex and this is often not well understood.
- Use of our Yellow Card scheme by the healthcare sector and members of the public is voluntary and it does not provide absolute AIR figures.
- AIR includes mandatory reporting by manufacturers for certain types of incidents as part of the regulatory (vigilance) process. It does not include Field Safety Notices or National Competent Authority Reports.
- Individuals may report an incident at any time after the event and people can make multiple reports at any time after the mesh has been implanted and on the same issue. Where possible, multiple reports for the same event are linked, however as reporters are not required to complete all fields, we cannot always be sure enough to link every duplicate.
- The 2 conditions and treatment of SUI and POP are quite different, any data for the various procedures for both should be considered independently and separately. A variety of different mesh repairs are used; and the outcomes may differ substantially for the two conditions. Therefore, we have separated the number of events by the indication of use.
- AIR data includes surgical mesh to treat SUI and POP by different surgical approaches and procedures within the scope of the Review (e.g., transvaginal and abdominal) We are unable to break this down as this is not a mandatory field in Yellow Card and may be unknown to the reporter.
- Some reports do not include the necessary information to determine the indication of use of the surgical mesh, but we have included them to give you the data we hold on these devices. These are identified as ‘unknown indication’.
- AIRs are from manufacturers, healthcare professionals and patients of events that occurred in the UK and reports do not necessarily represent an individual patient.
- Where the number of reports is low (less than 5) this has been indicated as '<5'. This is to comply with our confidentiality obligations because when the numbers of reports are low and if they are put together with other information, it might make the individual reports identifiable to specific patients or healthcare organisations.

Annex E: NICE Interventional Procedures Guidance for Q1

Of seven pieces of Interventional Procedures Guidance (see table overleaf), NICE has concluded that the evidence supports the procedure as safe and efficacious in two cases, warranting standard arrangements for governance, and has found that the risks associated with the procedure require special arrangements for clinical governance, consent and audit in the other five cases. A “Special Arrangements” recommendation does not imply the procedure should be restricted or should not be used.

Guidance on the repair of anterior and posterior vaginal wall prolapse and guidance on repair of apical prolapse of the uterus or vagina (pectopexy) concludes the long-term efficacy is inadequate in quality and quantity. Therefore, this procedure should only be used in the context of research.

The use of “Research Only” label also does not mean the procedure should not be used, but sets out the additional governance required, including what questions need to be answered moving forward. In this latter case this is to ensure longer term follow up is adequately studied to gain more evidence over time. This does not constitute a “back door ban”, but shows the procedures have a clinical place and need a greater body of evidence in the longer term to better understand efficacy and safety. The recommendations for are generally consistent with the Scottish Review and NHS E Oversight Group Report recommendation that vaginal mesh should not be routinely offered as the first surgical intervention when treating prolapse.

A Special Arrangements recommendation requires clinicians using the procedure to:

1. Inform the clinical governance lead in their trust that they are doing this procedure.
2. Tell the patient about uncertainties regarding the safety and efficacy of the procedure.
3. Collect further data by means of audit or research.

In general, the Committee will recommend Special Arrangements when some uncertainties in the evidence on efficacy or safety remain.

Information on other types of recommendation made by NICE are found here.

IPG number	Procedure Name	Publication Date	New recommendation	Summary (including reference to committee comments)	Previous arrangements	Relevance to TGA/MEDSAFE Decision Y/N
IPG583	Sacrocolpopexy using mesh to repair vaginal vault prolapse (Open/laparoscopic approach)	Jun-17	**Standard arrangements**	Current evidence on the safety of sacrocolpopexy using mesh to repair vaginal vault prolapse shows there are serious but well-recognised safety concerns. The evidence on efficacy is adequate in quantity and quality. Therefore, this procedure can be used provided that standard arrangements are in place for clinical governance, consent and audit. The 13 out of 14 women who returned the patient questionnaire would recommend this procedure. https://www.nice.org.uk/guidance/ipg583/chapter/1-Recommendations	**Standard arrangements**	**No**
IPG582	Infracoccygeal sacropexy using mesh to repair uterine prolapse (Transvaginal approach)	Jun-17	**Special arrangements**	Current evidence on the safety of infracoccygeal sacropexy using mesh to repair uterine prolapse shows there are serious but well recognised complications. The evidence on efficacy is inadequate in quality. Therefore, this procedure should not be used unless there are special arrangements in place for clinical governance, consent and audit or research.	**Special arrangements**	**Yes**

IPG number	Procedure Name	Publication Date	New recommendation	Summary (including reference to committee comments)	Previous arrangements	Relevance to TGA/MEDSAFE Decision Y/N
				This procedure is rarely done and has been replaced by laparoscopic techniques using mesh. https://www.nice.org.uk/guidance/ipg582/chapter/1-Recommendations		
IPG581	Infracoccygeal sacropexy using mesh to repair vaginal vault prolapse (Transvaginal approach)	Jun-17	**Special arrangements**	Current evidence on the safety of infracoccygeal sacropexy using mesh to repair vaginal vault prolapse shows there are serious but well-recognised complications. The evidence on efficacy is inadequate in quality. Therefore, this procedure should not be used unless there are special arrangements in place for clinical governance, consent, and audit or research. Use of this procedure is declining. https://www.nice.org.uk/guidance/ipg581/chapter/1-Recommendations	**Special arrangements**	**Yes**
IPG584	Uterine suspension using mesh (including sacrohysteropexy) to repair uterine prolapse	Jun-17	**Normal or standard arrangements**	Current evidence on the safety of uterine suspension using mesh (including sacrohysteropexy) to repair uterine prolapse shows there are serious and well-recognised complications. The evidence on efficacy is adequate in quantity and quality. Therefore, this procedure can	**Special arrangements**	**No**

IPG number	Procedure Name	Publication Date	New recommendation	Summary (including reference to committee comments)	Previous arrangements	Relevance to TGA/MEDSAFE Decision Y/N
	(Open/laparoscopic approach)			be used provided that standard arrangements are in place for clinical governance, consent and audit. Patient commentaries supported use of the procedure. https://www.nice.org.uk/guidance/ipg584/chapter/1-Recommendations		
IPG599	Transvaginal mesh repair of anterior or posterior vaginal wall prolapse (Transvaginal approach)	Dec-17	**Research**	Current evidence on the safety of transvaginal mesh repair of anterior or posterior vaginal wall prolapse shows there are serious but well-recognised safety concerns. Evidence of long-term efficacy is inadequate in quality and quantity. Therefore, this procedure should only be used in the context of research. Most commentaries received from patients reported satisfaction with the procedure and that it had worked and improved their quality of life. Randomised controlled trial data showed no added benefit of using mesh compared with native tissue repair. https://www.nice.org.uk/guidance/ipg599/chapter/1-Recommendations	**Special arrangements**	**Yes**

IPG number	Procedure Name	Publication Date	New recommendation	Summary (including reference to committee comments)	Previous arrangements	Relevance to TGA/MEDSAFE Decision Y/N
IPG566	Single-incision short sling mesh insertion for stress urinary incontinence in women (Transvaginal approach)	Oct-16	**Special arrangements**	IPAC's decision to change its recommendation on single-incision short sling mesh insertion for stress urinary incontinence in women from "research only" to "special arrangements" was, because in their view the procedure was no longer considered new and the level of uncertainty regarding efficacy and safety was deemed to no longer require scrutiny from a research ethics committee. The evidence on the safety of single-incision short sling mesh insertion for stress urinary incontinence in women shows infrequent but serious complications. These include lasting pain, discomfort and failure of the procedure. The mesh implant is intended to be permanent but, if removal is needed because of complications, the anchoring system can make the device very difficult or impossible to remove. The evidence on efficacy in the long term is inadequate in quality and quantity. Therefore, this procedure should not be used unless there are special arrangements in place for clinical	**Research**	**Yes**

IPG number	Procedure Name	Publication Date	New recommendation	Summary (including reference to committee comments)	Previous arrangements	Relevance to TGA/MEDSAFE Decision Y/N
				governance, consent, and audit or research. https://www.nice.org.uk/guidance/ipg566/chapter/1-Recommendations		
IPG577	Sacrocolpopexy with hysterectomy using mesh to repair uterine prolapse (Open/laparoscopic approach)	Mar-17	**Special arrangements**	Current evidence on the safety and efficacy of sacrocolpopexy with hysterectomy using mesh to repair uterine prolapse is inadequate in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research. Patient commentaries supported use of the procedure. Concomitant total hysterectomy with sacrocolpopexy is associated with a higher risk of mesh erosion when compared with concomitant subtotal hysterectomy with sacrocolpopexy. This may be because of the closeness of the mesh to a fresh suture line. https://www.nice.org.uk/guidance/ipg577/chapter/1-Recommendations	**Special arrangements**	**No**

IPG number	Procedure Name	Publication Date	New recommendation	Summary (including reference to committee comments)	Previous arrangements	Relevance to TGA/MEDSAFE Decision Y/N
IPG576	Extraurethral (non-circumferential) retropubic adjustable compression devices for stress urinary incontinence in women (perineal incision)	Mar-17	**Special arrangements**	Current evidence on the safety and efficacy of extraurethral (non-circumferential) retropubic adjustable compression devices for stress urinary incontinence in women is inadequate in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research. The committee was informed that the procedure is not in widespread use in the UK. https://www.nice.org.uk/guidance/ipg576/chapter/1-Recommendations	**Special**	**No**
IPG608	Laparoscopic mesh pectopexy for apical prolapse of the uterus or vagina (Laparoscopic approach)	Mar-18	**Research only**	Current evidence on the safety and efficacy of laparoscopic mesh pectopexy for apical prolapse of the uterus or vagina is insufficient in quality and quantity. Therefore, this procedure should only be used in the context of research. https://www.nice.org.uk/guidance/ipg608/chapter/1-Recommendations	**Research only**	**No**

Annex F: Additional Material for Q 24

Table 1

TNA REFERENCE	FILE TITLE	DATE	Full / Partial scan
BN 116/5	Committee on Safety of Medicines: meetings 1-12 (1974); minutes signed by the Chairman	1974 Jan 24 - 1974 Dec 19	Partial
BN 116/6	Committee on Safety of Medicines: meetings 1-12 (1975); minutes signed by the Chairman	1975 Jan 23 - 1975 Dec 18	Partial
BN 116/9	Committee on Safety of Medicines: meetings 3-12 (1977); minutes signed by the Chairman	1977 Mar 24 - 1977 Dec 15	Partial
BN 116/11	Committee on Safety of Medicines: meetings 8-12 (1978); minutes signed by the Chairman	1978 Aug 17 - 1978 Dec 14	Partial
BN 116/12	Committee on Safety of Medicines: Sub-Committee on Adverse Reactions; meetings 1-4 (1971); agendas, minutes and papers	1971 Jan 20 - 1971 Jul 14	Partial
BN 116/14	Committee on Safety of Medicines: Sub-Committee on Adverse Reactions; meeting 6 (1971); agenda, minutes and papers	1971 Nov 17	Partial
BN 116/15	Committee on Safety of Medicines: Sub-Committee on Adverse Reactions; meeting 1 (1972); agenda, minutes and papers	1972 Jan 19	Partial
BN 116/19	Committee on Safety of Medicines: Sub-Committee on Adverse Reactions; meetings 1-3 (1975); agendas, minutes and papers	1975 Jan 15 - 1975 May 21	Partial
BN 116/20	Committee on Safety of Medicines: Sub-Committee on Adverse Reactions; meetings 4-5 (1975); agendas, minutes and papers	1975 Jul 16 - 1975 Sep 17	Partial
BN 116/21	Committee on Safety of Medicines: Sub-Committee on Adverse Reactions; meetings 1-6 (1976); agendas and minutes	1976 Jan 14 - 1976 Nov 17	Partial
BN 116/24	Committee on Safety of Medicines: Sub-Committee on Adverse Reactions; meeting 6 (1977); agenda, minutes and papers	1977 Nov 16	Partial
BN 116/26	Committee on Safety of Medicines: Sub-Committee on Adverse Reactions; meeting 4 (1978); agenda, minutes and papers	1978 Jul 06	Partial

TNA REFERENCE	FILE TITLE	DATE	Full / Partial scan
BN 116/27	Committee on Safety of Medicines: Sub-Committee on Adverse Reactions; meetings 5-6 (1978); agendas, minutes and papers	1978 Sep 07 - 1978 Nov 02	Partial
BN 116/359	Committee on Safety of Medicines: Adverse Reactions Group of the Sub-Committee on Safety, Efficacy and Adverse Reactions (SEAR); meetings 1-4 (1984); agenda, minutes and papers	1984 Feb 10 - 1984 May 11	Partial
BN 116/365	Committee on Safety of Medicines: Adverse Reactions Group of the Sub-Committee on Safety, Efficacy and Adverse Reactions (SEAR); meetings 5-7 (1986); agenda and papers	1986 May 09 - 1986 Jul 11	Partial
BN 116/367	Committee on Safety of Medicines: Adverse Reactions Group of the Sub-Committee on Safety, Efficacy and Adverse Reactions (SEAR); meeting 9 (1986); agenda and papers	1986 Oct 10	Partial
MH 149/23	Standing Joint Committee on Classification of Proprietary Preparations - Working papers and minutes of meetings	1965	Partial
MH 171/18	Sub Committee on Adverse Reactions: notifications to committee of adverse reactions	01/01/1964 - 31/12/1964	Partial
MH 171/19	Sub Committee on Adverse Reactions: notifications to committee of adverse reactions	01/01/1965 - 31/12/1965	Partial
MH 171/20	Sub Committee on Adverse Reactions: notifications to committee of adverse reactions	01/01/1967 - 31/12/1967	Partial
MH 171/21	Sub Committee on Adverse Reactions: notifications to committee of adverse reactions	01/01/1970 - 31/12/1970	Partial
MH 171/31	Sub Committee on Adverse Reactions and Medical Research Council discussion papers: comparisons in incidence of reaction reports	01/01/1964 - 31/12/1971	Partial
MH 171/50	Committee on the Safety of Drugs; minutes of meetings signed by chairman Sir Derrick Dunlop - 1st to 11th meetings 1965	01/01/1965 - 31/12/1965	Partial
MH 171/61	Sub-Committee on Adverse Reactions: minutes of meetings; committee papers	1974	Partial

Five files that appeared to contain relevant information from the period January 1962 to December 1967 were marked ‘Missing at transfer’ and could not be recovered. The contents of these files are summarised below.

Table 2

TNA REFERENCE	**FILE TITLE**	**DATE**
MH 171/4	Sub Committee on Adverse Reactions: minutes of meetings, signed by Professor L J Witts - chairman	01/01/1966 - 31/12/1966
MH 171/5	Sub Committee on Adverse Reactions: minutes of meetings, signed by Professor L J Witts - chairman	01/01/1967 - 31/12/1967
MH 171/12	Sub Committee on Adverse Reactions: draft agendas, notes and correspondence	01/01/1966 - 31/12/1966
MH 171/51	Minutes of the meetings of the meetings signed by chairman Sir Derrick Dunlop (1st to 11th meetings 1966)	01/01/1966 - 31/12/1966
MH 171/57	Committee on Safety of Drugs: main committee correspondence	01/01/1962 - 31/12/1967

Sodium valproate: regulatory history relating to use in pregnancy

Date	Regulatory action
1971	Application for sodium valproate received.
1972	Application considered by CSM, decision initially deferred until further information was provided. Because of animal data which suggested a possible risk of birth defects, the Committee on Safety of Medicines (CSM) advised that a product licence for valproate should only be granted for one year; limited to hospitals and other centres specialising in the treatment of epilepsy. There was also consideration by the Sub-Committee on Chemistry, Pharmacy and Standards in January 1972, which evaluated manufacturing and batch release at the time of licensing. **(minutes in PDF annex, doc "A CSM Minutes January 1972", 'A CSM Minutes May 1972' and 'A CSM Minutes June 1972', A CPS minutes January 1972)**
1973	CSM recommended that warnings about birth defects be added to the datasheets for all anticonvulsants. CSM recommended that warnings about birth defects should not be put in package inserts. The minutes go on to say that possible risks with all anticonvulsants had been mentioned in a letter from the Chairman of the CSM to all doctors in May 1973. (**minutes in PDF annex, doc 'B. CSM Minutes June 1973', doc 'B. CSM Minutes July 1973' and doc 'B. CSM Minutes August 1973)**
1974	Following further consideration by CSM and the Adverse Reactions Sub-Committee*, valproate was marketed for general prescription in 1974 with warnings about the risk of birth defects and restrictions to use. (**minutes in PDF annex, doc 'C. CSM Minutes March 1974', 'C CSM Minutes August 1974' and 'C. CSM Minutes September 1974)** **(Core Data Sheet in PDF annex doc 'C. Core Data Sheet 1974')** *we are trying to retrieve the minutes from the National Archives.
1975	The first datasheet for valproate was published. This was aimed at prescribers and stated: *"In women of childbearing age, the product should only be used in severe cases or in those resistant to other treatment."* and *"This compound has been shown to be teratogenic in animals. Any benefit which may be expected from its use should be weighed against the hazard suggested by these findings."*
1976	Consideration by the Medicines Commission* on product advertising. *we are trying to retrieve the minutes from the National Archives.
1980	CSM considered a proposal for a study on congenital malformations. (**minutes in PDF annex, doc 'D. CSM Minutes 1980')**

1982	CSM considered a paper on sodium valproate and teratogenicity. Agreed there was a need for specific research into the role of anti-convulsant therapy in epileptic mothers in increasing the risks of congenital malformation of the foetus. The CSM agreed there should be an Article in Current Problems which should be issued as soon as possible. (**minutes in PDF annex, doc 'E. CSM Minutes November 1982' and 'E. CSM Minutes December 1982')**
1983	An article was published in the Medicines Control Agency's (MCA's) bulletin 'Current Problems' which was issued to healthcare professionals warning about sodium valproate (brand name Epilim) and birth defects. **(article in PDF annex doc F. CPIP 1983')**
1990	Additional information on Foetal abnormalities, specifically neural tube defects, and information on recommended diagnostic screening, added to product information.
June 1993	An article was published in the MCA's bulletin 'Current Problems in Pharmacovigilance' regarding neural tube defects (birth defects of the brain, spine or spinal cord) associated with valproate and carbamazepine including the need for counselling and screening of women. **(article in PDF annex doc G. CPIP 1993')**
1999	Patient information leaflets became a legal requirement for all medicines.
March 2001	A warning in product information that sodium valproate should only be used in women of childbearing potential in severe cases or in those resistant to other treatments was expanded to reflect the available evidence on the risk of birth defects and to state that women should be informed of the risks and benefits of continuing treatment.
27/11/02	Working Group on paediatric medicines discussed sodium valproate and developmental delay. The WG considered that there was now evidence from a number of studies suggesting an increased risk of developmental delay following in-utero exposure. Advised product information should be updated to include a warning. **minutes in PDF annex, doc 'H. Paediatric Medicines WG Nov 2002)**
04/2003	Warnings were added that *'Women of childbearing potential should not be started on Epilim without specialist neurological advice.'* Section 4.6 was changed to include malformation rates associated with epilepsy and anti-epileptics, an expanded list of malformations associated with valproate and frequency of spina bifida. Detailed advice was added on reviewing treatment, dosing advice if treatment continued and folate supplementation. Warnings about developmental delay were added: *"Epidemiological studies have suggested an association between in-utero exposure to sodium valproate and a risk of developmental delay. Many factors including maternal epilepsy may also contribute to this risk but it is difficult to quantify the relative contributions of these or of maternal antiepileptic treatment. Notwithstanding those potential risks, no sudden discontinuation in the anti-*

	epileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both the mother and the foetus."
09/2003	An article was published in the MHRA bulletin 'Current Problems in Pharmacovigilance' regarding sodium valproate and the risks associated with prescribing in pregnancy. **(article in PDF annex doc I. CPIP 2003')**
2010	EU Article 31 referral reviewing the safety and effectiveness of valproate in the treatment of manic episodes in bipolar disorder. The CHMP concluded that all marketing authorisations should be harmonised to include the treatment of manic episodes in bipolar disorders when lithium is contraindicated or not tolerated. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Valproate/human_referral_000187.jsp&mid=WC0b01ac0580024e9a
October 2010	Statement on increased risk versus other antiepileptics added: *'The data suggest that the use of valproate is associated with a greater risk of certain types of these malformations (in particular neural tube defects) than some other anti-epileptic drugs'.* A statement that *'Autistic spectrum disorders have also been reported in children exposed in utero'.* This was based on case reports and retrospective studies.
2011	US FDA warned of the possibility of impaired cognitive development in children born to mothers exposed to valproate in utero. As in the EU they advised women of child bearing potential should be counselled about the risks, advised of the need for contraception, and that alternative medicines should be considered**.** https://www.fda.gov/Drugs/DrugSafety/ucm261543.htm
March 2012	Denmark presented a summary of the most recent data on the neurodevelopmental effects of in utero exposure to valproate to the EU Pharmacovigilance Working Party (PhVWP). In the UK, this subject generated significant parliamentary and media interest. During 2012/13 the MHRA was contacted on multiple occasions by several contacts in patient support groups calling for action to update warnings and issue further communications.
March 2013	Signal of sustained neurodevelopmental disorders discussed at PRAC (successor to PhVWP). Denmark was lead Member State but indicated they did not have resource to look at the new data. MHRA offered assistance.
June 2013	CPRD data extracted and analysed on the rate of prescribing of valproate and other anti-epileptics in women of child bearing potential and pregnancy. Signal discussed again at PRAC. MHRA interviewed by Panorama.
21/06/13	Submission sent to Ministers with regards to Panorama programme.
01/07/13	Panorama airs. https://jocuz1971.wordpress.com/2013/06/29/panorama-feature-fetal-valproate-syndrome/

02/08/13	Protest outside MHRA office by FACS aware. http://jocuz1971.wordpress.com/2013/07/25/demonstration-outside-the-mhra-2nd-august-2013-1-pm/
16/08/13	Patient group (INFACT) attend meeting with MHRA – they raise concerns and present their survey data on the awareness of risks. MHRA provide email feedback to INFACT on survey. Action taken forward to review Yellow Card with regards to capturing adverse events associated with exposure in-utero.
09/2013	NUI (Non Urgent Information) request sent out by UK to ask all MSs about National licences and text on neurodevelopmental delay in the product information.
02/10/13	Pharmacovigilance Expert Advisory Group paper, which included full literature review. The EAG was presented with a summary assessment of the latest published study data on the risk of longer term potential neurodevelopmental effects, including autistic spectrum disorder, following foetal valproate exposure. EAG advised that an EU referral should be triggered to fully evaluate the impact of the new data. **(Minutes in PDF annex doc 'J. PEAG mins October 2013')**
07/10/13	Data published in 2013 allowed more robust evaluation of any possible risk of longer term neurodevelopmental effects. UK initiated an Article 31 Referral on the basis of the following: **Key studies:** Meador et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol. 2013 Mar;12(3):244-52. Bromley R et al. The prevalence of neurodevelopmental disorders in children prenatally exposed to antiepileptic drugs. J Neural Neurosurgery Psychiatry 2013;0:1-7 Christensen J et al. Association of sodium valproate with risk of autism spectrum disorders and childhood autism. JAMA, April 24, 2013.Vol 309,16. Veiby, Gyri et al. Exposure to aniepeileptic drugs in utero and child development. A prospective population-based study. Epilepsia.2013. Aug 54(8): 1462-72. **Key findings**: IQ deficits persist to the age of 6 years, are independent of maternal IQ and there is a risk of autism spectrum disorder and childhood autism with data in Christensen including some children followed up to age 14 years. Discussion at PRAC following triggering of referral. Netherlands lead Member State, UK supporting Member State**.** http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2013/11/WC500154424.pdf
29/10/13	Minister met a delegation led by Anas Sarwar MP to discuss Fetal Anti-Convulsant Syndrome (FACS). Alec Shelbrooke MP, Chair of the All-Party Group on Thalidomide, was also present, with a number of affected parents representing the various support groups and a young person who is herself affected by FACS.
14/11/13	A reminder article was published in the bulletin 'Drug Safety Update' reminding healthcare professionals about the risk of birth defects and possible risk of developmental delay associated with use of sodium

	valproate. https://www.gov.uk/drug-safety-update/sodium-valproate-risk-of-neurodevelopmental-delay-in-children-following-maternal-use
09/12/13	DH submission and draft letter sent to Ministers following meeting on 29 October 2013 with a delegation led by Anas Sarwar MP to discuss Fetal Anti-Convulsant Syndrome (FACS).
06/01/14	DH hosted meeting on prescribing of Anti-Epileptic drugs to pregnant women. Attendees included MHRA, Royal Pharmaceutical Society, the National Clinical Director for Neurological Conditions and a pharmacist from Maternity Services at Guys and St Thomas's Hospital.
20/01/14	DH submission to Ministers to update on action being taken to improve awareness of the potential effects of prescribing anti-epileptic drugs to pregnant women.
26/02/14	First meeting of the CHM Sodium Valproate Working Group. Advice sought in relation to ongoing EU review. **(minutes in PDF annex doc K. CHM sodium Valproate WG February 2014')**
28/03/14	DH officials met partners including the National Clinical Director for Maternity and Women's Health, MHRA representatives and clinicians from psychiatry services and general practice to discuss the impact of the prescribing of sodium valproate to women of childbearing age, for both neurological and mental health conditions.
08/04/14	Update from MHRA to DH about discussions at the Pharmacovigilance Risk Assessment Committee (PRAC).
14/04/14	Update to DH from MHRA on progress of European referral.
April 2014	Yellow Card updated to collect information about drug exposure in utero.
18/06/14	Second meeting of the CHM Sodium Valproate Working Group. Advice sought in relation to ongoing EU review. **(minutes in PDF annex doc L. CHM sodium Valproate WG June 2014')**
21/11/14	Following the EU review CMDh agrees to strengthen warnings on the use of valproate in women and girls. https://www.ema.europa.eu/documents/press-release/cmdh-agrees-strengthen-warnings-use-valproate-medicines-women-girls_en.pdf
21/11/14	Submission to Ministers on conclusions of EU review of use of valproate during pregnancy. Parallel submission sent from DH on raising awareness of the issue with health professionals and patients.
8/12/14	Email from Minister noting the submission.
11/12/14	CHM considered conclusions of EU review. **(minutes in PDF annex doc 'M CHM Minutes December 2014')**

15/01/15	Submission to Ministers on CHM advice on implementation of the EU conclusions.
21/01/15	Following the EU review, a letter was sent to healthcare professionals and patient groups regarding the strengthened warnings regarding developmental disorders associated with use of sodium valproate during pregnancy. https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=102287
22/01/15	Article published in DSU - Children exposed in utero to valproate are at a high risk of serious developmental disorders (in up to 30-40% of cases) and/or congenital malformations (in approximately 10% of cases). https://www.gov.uk/drug-safety-update/medicines-related-to-valproate-risk-of-abnormal-pregnancy-outcomes
27/01/15	Response from Minister noting the submission.
03/07/15	Meeting between MHRA and the Association of British Neurologists (ABN) on the prescribing of valproate.
21/07/15	George Freeman and Jeremy Hunt met INFACT, Nick Dobrik, Teresa Pearce MP and Ivan Lewis MP.
07/09/15	Submission to Ministers to follow up on actions from the meeting on 21 July 2015.
15/09/15	Response from Minister noting the submission of 7 September 2015.
19/10/15	Minister for Life Sciences chairs the first round table meeting with key stakeholders. The aim of the meeting was to agree measures to drive forward compliance with prescribing restrictions for sodium valproate and ensure that women treated with valproate are fully aware of the risks in pregnancy.
27/10/15	Meeting between MHRA, DH and the Royal College of GPs to follow up on actions from meeting with Minister on 19 October 2015.
23/11/15	Meeting between MHRA, DH and NHS England to follow up on actions from meeting with Minister on 19 October 2015.
09/12/15	Minister chairs round table meeting with key stakeholders. The meeting discussed proposals from Sanofi for a package label warning and patient card to be distributed by pharmacists. The proposals were endorsed in principle. The other strand of work involves alerts on GP IT systems and this is running to a longer time frame. NHSE and HSCIC colleagues tasked with taking this forward.
08/01/16	Meeting with Patient Groups to discuss communications.
27/01/16	Minister chairs a round table meeting with key stakeholders. The aim of this meeting was to finalise plans for communication on the risks of valproate in pregnancy.

01/2016	MHRA worked with Sanofi and Valproate Stakeholder Network to develop the “toolkit”- patient card, a healthcare professional booklet, a patient guide, checklist for prescribers and a prominent warning on the outer packaging to say that the product could damage an unborn child.
04/02/16	Submission to ministers following roundtable meeting on 27 January 2016 to discuss plans for the launch of the new valproate communications toolkit.
09/02/16	Response from Minister noting the submission.
02/2016	Article in DSU **(**https://www.gov.uk/drug-safety-update/valproate-and-of-risk-of-abnormal-pregnancy-outcomes-new-communication-materials**)** and Toolkit and DHPC sent through the Central Alerting System (CAS) to GPs which included a link to online versions of the materials and asked them to identify women of childbearing age already taking valproate and ensure that a medication review is arranged with a specialist. NICE updated their epilepsy guideline in February 2016 to link to the MHRA’s Toolkit to ensure female patients are better informed about the risks of taking valproate during pregnancy. https://www.nice.org.uk/guidance/cg137
15/04/16	Meeting of the VSN and MHRA meet with ABN.
05/05/16	Meeting between MHRA, Sanofi and the Royal College of Paediatrics and Child Health (RCPCH) to discuss the availability of age-appropriate materials for children and young people on valproate.
13/06/16	Minister chairs a round table meeting with key stakeholders.
06/2016	The label warning on the outer packaging of valproate products began appearing in pharmacies from June 2016.
10/2016	Joint MHRA/RCGP learning video was released to raise awareness of the toolkit amongst GPs. YouTube channel.
19/12/16	Update submission sent ahead of meeting with Norman Lamb MP on 24 January 2017.
16/02/17	Meeting of the VSN to review what has already been done to promote the valproate communications toolkit and then to agree the next steps required to improve its dissemination and, ultimately, to achieve a significant reduction in prescribing figures.
22/02/17	Minister met with Norman Lamb MP and INFACT.
08/03/17	France notified a referral to review existing risk minimisation. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2014/03/event_detail_000918.jsp&mid=WC0b01ac058004d5c3
06/04/17	Joint NHSI/MHRA Patient Safety Alert issued via the CAS. https://www.gov.uk/drug-safety-update/valproate-and-developmental-disorders-new-alert-asking-for-patient-review-and-further-consideration-of-risk-minimisation-measures

05/07/17	Submission to Ministers to inform of the French decision to contraindicate sodium valproate in bipolar disorder (but not epilepsy) for women of child bearing potential and not using effective contraception.
07/2017	France contraindicated valproate-based drugs in psychiatry for pregnant women and women of child-bearing age who are not using effective contraception.
07/2017	Sanofi redistributed the hard copies of toolkit materials to GPs, specialist prescribers and pharmacists.
18/07/17	Update submission on valproate following request from Minister.
02/08/17	Meeting of the CHM Sodium valproate Expert Working Group (EWG). **(minutes in PDF annex doc 'N. Sodium valproate EWG mins August 2017')**
25/08/17	Joint version of the MHRA/RCGP learning video jointly badged with the RCP issued.
20/09/17	Submission sent to Ministers to inform about the public hearing being held at the European Medicines Agency on 26 September about managing the risks of sodium valproate in women of childbearing potential.
26/09/17	Public hearing held at EMA about managing the risks of sodium valproate in women of childbearing potential. http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_001432.jsp&mid=WC0b01ac0580a221a4
27/09/17	Response from minister noting the submission.
31/10/17	Meeting of the EWG. The EWG advised that a pregnancy prevention programme should be implemented and there should be a contraindication in women of child bearing potential unless on effective contraception. **(minutes in PDF annex doc 'O. Sodium valproate EWG mins October 2017')**
27/11/17	PRAC consideration continues. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/11/news_detail_002863.jsp&mid=WC0b01ac058004d5c1
01/12/17	Meeting of the Valproate Stakeholders Network (VSN). The VSN was informed of the new regulatory restrictions proposed for valproate – that valproate should be contraindicated in pregnancy and in women of childbearing potential not using effective contraception for both the epilepsy and bipolar disorder indication and that this should be underpinned by a pregnancy prevention plan. The VSN agreed that 3 strands of work should be taken forward in January to further consider the detail of the bespoke pregnancy prevention programme for valproate; prescribing protocols and informed consent/acknowledgement of risk forms and changes required to the packaging, including pack size and pictograms.

07/12/17	Advice of the Expert Working Group presented to CHM **(minutes in PDF annex doc 'P. CHM Minutes December 2017)**
07/12/17	Minister met with Chair and secretariat of the APPG on Sodium Valproate.
11/01/18	Minister met with members of the APPG on Sodium Valproate
22/01/18	VSN sub group meetings held. Output will feed into the ongoing EU referral and will be considered by the CHM Ad Hoc Expert Group on valproate on 31 January.
31/01/18	CHM EWG meeting.
22/02/18	Submission to Ministers on progress with the EU review and to inform of a divergent opinion from the the UK and Ireland with the proposed provision that a woman planning pregnancy who cannot switch to another anti-epileptic medication may continue with valproate if she makes an informed decision following counselling.
23/02/18	Meeting of the VSN to: • Update on the EU review of valproate in pregnancy and risk minimisation measures • Discuss the UK national actions to support implementation of new regulatory measures • Review the communication plans so far • Seek agreement on the actions stakeholders will undertake to support the regulatory action
23/02/18	Meeting with Sanofi to discuss implementation plans for labels, leaflets and educational materials.
27/02/18	Response from Minister noting the submission.
14/03/18	Ministerial stocktake meeting with MHRA, Royal Colleges and NHS England.
19/03/18	Submission to Ministers on communicating the outcome of the EU Review.
20/03/18	Response from Minister's office on the submission.
21/03/18	VSN meeting.
29/03/18	CHM EWG meeting. **(minutes in PDF annex doc 'Q. Sodium valproate EWG mins March 2018)**
04/04/18	VSN asked to comment on patient guide, patient card, and patient DSU sheet.
09/04/18	Submission to Ministers on plans for communicating the new strengthened valproate measures.
17/04/18	Response from Minister's office on the submission.

18/04/18	Behavioural Insights Team asked to consult on Pregnancy Prevention Plan (PPP) materials and planned communication plan.
18/04/18	Telecon with the Health Products Regulatory Authority (HPRA), Ireland, to share comments from VSN and EWG and to inform of planned communications.
19/0418	Telecon with RCGP about barriers for new strengthened valproate measures.
19/04/18	Letter sent to APPG about upcoming communications.
24/04/18	Communications issued. CEM_CMO_2018_001 Valproate.pdf https://www.gov.uk/drug-safety-update/valproate-medicines-epilim-depakote-contraindicated-in-women-and-girls-of-childbearing-potential-unless-conditions-of-pregnancy-prevention-programme-are-met https://www.parliament.uk/business/publications/written-questions-answers-statements/written-statement/Commons/2018-04-24/HCWS640/
02/05/18	VSN meeting held.
17/05/18	CHM EWG meeting. **(minutes in PDF annex doc 'R. Sodium valproate EWG mins May 2018)**
31/05/18	European Commission Decision http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Valproate_and_related_substances/human_referral_prac_000066.jsp&mid=WC0b01ac05805c516f
19/06/18	Ministerial meeting with clinical leads.
04/07/18	First letters with packs of PPP materials sent by Sanofi to pharmacists with DHPC. https://www.medicines.org.uk/emc/rmm/425/Document
16/07/18	First letters with packs of PPP materials sent by Sanofi to specialists, GPs, and other healthcare professionals with DHPC. https://www.medicines.org.uk/emc/rmm/1231/Document
25/07/18	VSN meeting.
17/08/18	Letter from the Epilepsy Society about the effectiveness of the communications.
21/08/18	Letter from INFACT to Minister raising concern about the implementation of the valproate warning and PPP.
26/09/18	MHRA wrote to the General Pharmaceutical Council, the General Medical Council and the Care Quality Commission about evidence of a lack of compliance with the PPP.

26/09/18	MHRA wrote to NICE asking them to take forward the work on development of a cross-disciplinary valproate guideline.
26/09/18	MHRA met with the Organisation for Anti-Convulsant Syndrome (OACS) so they could share their ideas on how they would support the new regulatory measures.
28/09/18	Submission updating on progress sent to Minister.
10/10/18	MHRA met with Sanofi to take stock of progress with implementation of the PPP.
17/10/18	MHRA presented to the APPG Annual General Meeting on the PPP.
22/10/18	The MHRA and four Chief Pharmaceutical Officers wrote to pharmacists on 22 October 2018 emphasising that all dispensed medicines containing valproate should be accompanied by a statutory patient information leaflet. https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=102805

COMMITTEE ON SAFETY OF MEDICINES

MINUTES OF THE MEETING HELD ON THURSDAY, 27 JANUARY 1972.

PRESENT:

Professor E F Scowen (Chairman)
Professor W I Cranston
Professor C T Dollery
Dr D C Garratt
Sir Austin Bradford Hill
Professor D R Laurence
Dr M J Linnett
Professor P N Magee
Professor D V W Parke
Professor Linford Rees
Professor J S Scott
Professor J B Stenlake
Dr D Mansel-Jones (Medical Assessor)
Mr S F Hall (Pharmaceutical Assessor)
Mr J B Brown (Secretary)

ALSO PRESENT:

[redacted] — Department of Health and Social Security; Committee Secretariat

CONTENTS

1. Apologies for absence
2. Minutes of the meeting held on 30 December 1971
3. Matters arising from the minutes
4. [redacted]
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0/0523/0001
0/0623/0002

Pharmacy Products UK Ltd

Tabazene Tablets
" Solution

(Anti-Convulsant)

Sub-Committee on Toxicity and Clinical Trials

The Sub-Committee recommends that a decision on these products should be deferred pending discussion with the applicants as to whether they would be prepared to conduct clinical trials comparing the product with phenytoin, since evidence of efficacy and safety in the clinical studies is inadequate.

Remarks

Further toxicological and teratological data is also required.

Main Committee

The Committee agreed that a decision on these products should be deferred pending discussion with the applicants as to whether they would be prepared to conduct clinical trials comparing the product with phenytoin, since evidence of efficacy and safety in the clinical studies is inadequate.

Subject to the applicant being willing to undertake a clinical trial on the lines indicated, then issue of a certificate could be recommended without further reference to the Committee.

NOT FOR PUBLICATION

Committee on Safety of Medicines

Sub-Committee on Chemistry, Pharmacy and Standards

Minutes of meeting held on Friday 28 January 1972

Present:	Professor J B Stenlake	(Chairman)
	Dr V Askam	
	Dr W R L Brown	
	Dr A T Florence	
	Dr D C Garratt	
	Mr Hadgraft	
	Professor M W Partridge	
	Dr Williams	
	Mr S F Hall	(Pharmaceutical Assessor)
	Miss M C Cone	(Secretary)

Also Present:

[redacted] (BP Commission, DHSS)
(Laboratory of the Govt Chemist)
(Committee Secretariat)

The Committee was reminded of the need to treat as confidential all information that came before them in the course of the business.

[redacted]

1. Apologies for absence

[redacted]

2. Minutes of the meeting held on December 31 1971

The minutes were agreed and signed by the Chairman.

3. Consideration of Applications for Manufacturers

[redacted]

Sub-Committee on Chemistry, Pharmacy and Standards

PL/0623/0001 - Labazene Tablets (Pharmacy Products UK Limited)

Remarks

1. Palladium catalyst is used during manufacture. Information on the palladium level in the drug substance should be given.

2. Batch analyses of three recent production batches should be supplied.

3. It was noted that the tablets will be packed in strip packs. There is no information on the type of packaging and the name and address of the proposed assembler in the UK is not given.

Recommendation

Satisfactory for marketing.

CSM/72/5th Meeting

NOT FOR PUBLICATION

COMMITTEE ON SAFETY OF MEDICINES

MINUTES OF THE MEETING HELD ON THURSDAY 25 MAY 1972

PRESENT:

Professor E F Scowen (Chairman)
Professor W I Cranston
Professor T Crawford
Professor R H Girdwood
Sir Austin Bradford Hill
Professor D R Laurence
Professor P N Magee
Professor W W Mushin
Professor D V W Parke
Professor W Linford Rees
Professor J B Stenlake
Dr D Mansel-Jones (Medical Assessor)
Mr S F Hall (Pharmaceutical Assessor)
Mr J B Brown (Secretary)

ALSO PRESENT:

[redacted]) DHSS
) Committee Secretariat

CONTENTS

1. Apologies for absence.
2. Minutes of the meeting held on 27 April 1972 and of the special meeting held on 5 May 1972.
3. Matters arising from the minutes.
4. Consideration of applications for Certificates and Licences.
5. Applications previously deferred.
6. Applications subject to outstanding Section 21(1) procedure.
7. Medical Assessor's report.
8. Exemptions from licensing.
9. Minutes of the Sub-Committees.
10. Other business.
11. Date and time of next meeting.

APPENDICES

A. Summary of recommendations on applications.

B. Minor applications recommended for issue of certificates or grant of licences.

C. Hearings: [redacted]

[redacted]

5. APPLICATIONS PREVIOUSLY DEFERRED (CSM/72/26)

The Committee was informed that further information had been provided on four applications, consideration of which had previously been deferred:

[redacted]

PL/0623/0001 - Pharmacy Products - Labazene Tablets

PL/0623/0002 - Pharmacy Products - Labazene Solution

Supplementary reports on these were before the Committee. Notes of discussion and the Committee's advice on these applications are included in Appendix A.

6. APPLICATIONS SUBJECT TO OUTSTANDING SECTION 21(1) PROCEDURE (CSM/72/54)

[redacted]

PL/0623/0001
PL/0623/0002

Pharmacy Products UK Ltd

Labazene Tablets
" Solution
(Anti-Convulsant)

Sub-Committee on Toxicity and Clinical Trials (January 1972)

The Sub-Committee recommends that a decision on these products should be deferred pending discussion with the applicants as to whether they would be prepared to conduct clinical trials comparing the product with phenytoin, since evidence of efficacy and safety in the clinical studies in inadequate.

Remarks

Further toxicological and teratological data is also required.

Main Committee (January 1972)

The Committee agreed that a decision on these products should be deferred pending discussion with the applicants as to whether they would be prepared to conduct clinical trials comparing the product with phenytoin, since evidence of efficacy and safety in the clinical studies is inadequate.

Subject to the applicant being willing to undertake a clinical trial on the lines indicated, then issue of a certificate could be recommended without further reference to the Committee.

Sub-Committee on Toxicity and Clinical Trials (May 1972)

On the evidence before them the Sub-Committee are unable to advise the grant of product licences for these preparations for the purposes indicated in the applicatio since the animal toxicology, including teratology, provided is inadequate and the data which has been presented gives ground for concern in view of the expected long term administration of the drug.

Main Committee (May 1972)

The Committee decided that consideration of this application should be deferred pending further discussion with the applicant regarding the possibility of a clinical trial being undertaken in an epileptic centre in the United Kingdom.

NOT FOR PUBLICATION

COMMITTEE ON SAFETY OF MEDICINES

MINUTES OF THE MEETING HELD ON THURSDAY 22 JUNE 1972

PRESENT:

Professor E F Scowen (Chairman)
Professor T Crawford
Dr D C Garratt
Professor R H Girdwood
Sir Austin Bradford Hill
Professor D R Laurence
Professor P N Magee
Professor D V V Parke
Professor W Linford Rees
Professor J S Scott
Professor J B Stenlake
Dr D Monsel-Jones
(Medical Assessor)
Mr S F Hall
(Pharmaceutical Assessor)
Mr J B Brown
(Secretary)

ALSO PRESENT:

[redacted] DHSS

[redacted] Committee Secretariat

CONTENTS

1. Apologies for absence
2. Minutes of the meeting held on 25 May 1972
3. Matters arising from the minutes
4. Consideration of applications for Certificates and Licences
5. Applications previously deferred
6. Applications subject to outstanding Section 21(1) procedure
7. Medical Assessor's Report
8. Confidentiality of information supplied under the provisions of the Medicines Act
9. Minutes of the Sub-Committees
10. Other business
11. Date and time of next meeting

APPENDICES

A. Summary of recommendations on applications

B. Minor applications recommended for issue of certificates or grant of licences

4. CONSIDERATION OF APPLICATIONS FOR CERTIFICATES AND LICENCES

[redacted]

5. APPLICATIONS PREVIOUSLY DEFERRED (CSM/72/26)

The Committee was informed that further information had been provided on six applications, consideration of which had previously been deferred:-

[redacted]

PL/0623/0001 - Pharmacy Products (UK) Ltd - Labazene Tablets

PL/0623/0002 - Pharmacy Products (UK) Ltd - Labazene Solution

Supplementary reports on these were before the Committee. Notes of discussion and the Committee's advice on these applications are included in Appendix A.

6. APPLICATIONS SUBJECT TO OUTSTANDING SECTION 21(1) PROCEDURE (CSM/72/60)

[redacted]

PL/0623/0001
PL/0623/0002

Pharmacy Products UK Ltd

Labazone Tablets
" Solution

(Anti-Convulsant)

Sub-Committee on Toxicity and Clinical Trials (January 1972)

The Sub-Committee recommends that a decision on these products should be deferred pending discussion with the applicants as to whether they would be prepared to conduct clinical trials comparing the product with phenytoin, since evidence of efficacy and safety in the clinical studies is inadequate.

Remarks

Further toxicological and teratological data is also required.

Main Committee (January 1972)

The Committee agreed that a decision on these products should be deferred pending discussion with the applicants as to whether they would be prepared to conduct clinical trials comparing the product with phenytoin, since evidence of efficacy and safety in the clinical studies is inadequate.

Subject to the applicant being willing to undertake a clinical trial on the lines indicated, then issue of a certificate could be recommended without further reference to the Committee.

Sub-Committee on Toxicity and Clinical Trials (May 1972)

On the evidence before them the Sub-Committee are unable to advise the grant of product licences for these preparations for the purposes indicated in the application since the animal toxicology, including teratology provided is inadequate, and the data which has been presented gives ground for concern in view of the expected long term administration of the drug.

Sub-Committee on Toxicity and Clinical Trials (June 1972)

Tablets - PL/0623/0001

On the evidence before them the Sub-Committee recommend the grant of a product licence for one year for this preparation for the purposes indicated in the application provided that promotion is limited to hospitals and other centres specialising in the treatment of epilepsy, and subject to all patients being monitored for therapeutic efficacy and safety.

Solution - PL/0623/0002

The Sub-Committee recommend that a decision on this product should be deferred pending the outcome of discussions between the Sub-Committee on Chemistry and Pharmacy and the applicant on the question of the "dropper" for use with this preparation.

(continued on page 18a)

PL/0623/0001
PL/0623/0002

Pharmacy Products UK Ltd

Labazene Tablets
" Solution

(An-i-Convulsant)

Main Committee (June 1972)

Tablets - PL/0623/0001

On the evidence before them the Committee advise the grant of a product licence for one year for this preparation for the purposes indicated in the application, provided that promotion is limited to hospitals and other centres specialising in the treatment of epilepsy, and subject to all patients being monitored for therapeutic efficacy and safety. The Committee also advise that this product should be regarded as new for the purpose of a special directive for the reporting of adverse reactions.

Solution - PL/0623/0002

The Committee noted that the applicant did not wish to proceed at this time with the Solution.

NOT FOR PUBLICATION CSM/73/ 6th Meeting

COMMITTEE ON SAFETY OF MEDICINES

MINUTES OF THE MEETING HELD ON THURSDAY 28 JUNE 1973

Present:		Also Present:	
Sir Eric Scowen (Chairman)	)	[redacted]	)
Professor W I Cranston	)		) DHSS.
Dr D C Garratt	)		)
Professor R H Girdwood	)		
Sir Austin Bradford Hill	)		) SHHD
Dr M J Linnett	)		
Professor W W Mushin	)		
Professor D V W Parke	)		
Professor J S Scott	)		
Professor J B Stenlake	)		
Dr J A Holgate (Acting Medical Assessor)	)		
Mr S F Hall (Pharmaceutical Assessor)	)		) Committee Secretariat
Mr J B Brown (Secretary)	)		)

CONTENTS

1. Apologies for absence
2. Minutes of the Meeting held on 24 May 1973
3. Matters arising from the minutes
4. Consideration of Applications
5. Applications Previously Deferred
6. Applications subject to Section 21(1) or Schedule 2(2) procedure
7. Medical Assessor's Report
8. Drug Formulations - the need for more information
9. Anticonvulsant Teratogenicity
10. [redacted]
11. [redacted]
12. [redacted]

[redacted]

9. ANTICONVULSANT TERATOGENICITY (CSM/73/65)

The Committee noted and welcomed the action proposed by ICI Ltd with regard to modification of the data sheet on Mysoline to include a statement about the incidence of congenital abnormalities in infants born of epileptic mothers. They did not however think that the evidence was as yet sufficiently conclusive for the inclusion of such a statement to be advised as a general condition in association with the licensing of all anticonvulsant preparations.

10. [redacted]

NOT FOR PUBLICATION

CSM/73/ 7th Meeting

COMMITTEE ON SAFETY OF MEDICINES

MINUTES OF THE MEETING HELD ON THURSDAY 26 JULY 1973

Present:

Sir Eric Scowen (Chairman)
Professor W I Cranston
Sir Theo Crawford
Professor C T Dollery
Professor D G Evans
Dr D C Garratt
Sir Austin Bradford Hill
Professor D R Laurence
Professor W Linford Rees
Professor W W Mushin
Professor J B Stenlake
Dr D Mansel-Jones (Medical Assessor)
Mr S F Hall (Pharmaceutical Assessor)
Mr J B Brown (Secretary)

Also Present:

[redacted] — DHSS

Committee Secretariat

CONTENTS

1. Apologies for absence
2. Minutes of the Meeting held on 28 June 1973
3. Matters arising from the minutes
4. Consideration of Applications
5. Applications Previously Deferred
6. Applications subject to Section 21(1) or Schedule 2(2) procedure
7. Medical Assessor's Report
8. EEC draft directives and proposed directives relating to the marketing of proprietary medicinal products
9. Minutes of the Sub-Committees

2. MINUTES OF THE MEETING HELD ON 28 JUNE 1973.

These were agreed and signed by the Chairman.

3. MATTERS ARISING FROM THE MINUTES

[redacted]

3.3 Anticonvulsant Teratogenicity (minute 9 of 73/6)

The Committee was informed that the Sub-Committee on Adverse Reactions had accepted the Main Committee's view that it would be best not to mention the possibility of congenital abnormality following the use of anticonvulsants in relevant package inserts. The Sub-Committee had still felt, however, there was a case for a mention to be made in data sheets to ensure that doctors were aware of the hazard, in part because of the possibility of litigation. Whilst the Committee was sympathetic to this view they thought in practice it would be extremely difficult to make certain that the statement was included in all the relevant data sheets for the wide range of products containing anticonvulsant substances.

There was the added complication that for substances such as phenobarbitone there was little or no promotional activity on the part of the manufacturers and thus little likelihood of data sheets for products containing them. As the matter had been mentioned in the Chairman's letter sent to all doctors in May 1973 the Committee felt that reasonable steps had already been taken to see that the profession was alerted to the hazard, and that in the light of this the Sub-Committee would not consider it necessary to press for any further action.

3.4 [redacted]

NOT FOR PUBLICATION

CSM/73 8th Meeting

COMMITTEE ON SAFETY OF MEDICINES

MINUTES OF THE MEETING HELD ON THURSDAY 30 AUGUST 1973

Present:		Also Present:	
Sir Eric Scowen	(Chairman)	[redacted]	
Professor D G Evans			
Professor R H Girdwood			DHSS
Sir Austin Bradford Hill			
Professor D R Laurence			
Professor W Linford Rees			
Dr M J Linnett			
Professor W W Mushin			
Professor D V W Parke			
Professor J S Scott			
Professor J B Stenlake			
Dr E L Harris	(Acting Medical Assessor)		
Mr S F Hall	(Pharmaceutical Assessor)		
Mr F A S Middleton	(Acting Secretary)		Committee Secretariat

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1. Apologies for absence.
2. Minutes of the Meeting held on 26 July 1973.
3. Matters arising from the minutes.
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5. Applications subject to Section 21(1) or Schedule 2(2) procedure.
6. Medical Assessor's Report.
7. Dental Materials.
8. Proposed Temporary Section 62 Order.
9. Other business.
10. Date and time of next meeting.

[redacted]

3.2 Anticonvulsant Teratogenicity (Minute 3.3 of 73/7)

The Chairman reminded the Committee of the Sub-Committee's recommendation that all anticonvulsants should have an associated warning regarding possible teratogenicity. The Committee's views regarding the difficulties this presented had been conveyed to the Sub-Committee but they still felt the evidence sufficiently strong to call for some action on the matter. In due course the Sub-Committee would be submitting for consideration a report on the results of their survey of congenital abnormalities which was now being conducted on their behalf. Comment on the teratogenicity of anticonvulsants would of course be included in the report. Publication of the report would help to draw attention to the hazards of anticonvulsant treatment. The Chairman said that he had, however, discussed the matter with Sir Richard Doll, who had thought some earlier publicity would be welcomed by his Sub-Committee. He had therefore agreed to discuss the question of how this might best be achieved with Dr Cameron of the BMA, with a view to ensuring that all doctors were alerted to the hazards, yet without creating undue alarm.

DATA SHEET

NAME OF PRODUCT

Epilim

PRESENTATION

Epilim is available as a scored white tablet with a diameter of 11mm. The active ingredient is Sodium Valproate (200mg per tablet).

USES

For use in generalised, focal or other epilepsy (e.g. Petit Mal, Grand Mal, Mixed and other Psychomotor epilepsy).

In fertile women inadequately controlled by other therapies, the probable benefits of Epilim should be weighed against the possible hazard during early pregnancy suggested by laboratory experiments in animals (see Precaution - Women of Childbearing Age).

DOSAGE AND ADMINISTRATION

Adults and Children over 15 yrs.

Epilim can be introduced alone or added to existing treatment.

New Patients:
Treatment should start with 1 tablet three times daily. Dosage may be increased after three days to 2 tablets three times daily. If, after a total period of two weeks, adequate control has not been achieved, dosage of Epilim should again be increased and one other anti-epileptic agent may be introduced, commencing at a low dosage. Dosage of both Epilim and other agents should then be adjusted during the stabilisation period to obtain optimum control.

Patients receiving other Therapy:
Treatment should start with 1 tablet twice a day. Dosage can be increased at intervals of three days in increments of two tablets per day; optimum control is achieved usually within the dosage range of 4-7 tablets (800-1,400mg) per day. (However in several recently published controlled trials, it was found that the dose could be increased with advantage to 2.4g per day to achieve control in very severe cases).

Dosage of existing medication may be reduced concomitantly to obtain optimum control on a minimum dosage combination of drugs. It may be possible to withdraw the concomitant therapy allowing optimum control with Epilim alone (e.g. in Petit Mal with absence). If increased sedation is observed, dosage of barbiturates should be concomitantly reduced as the dosage of Epilim is increased.

Tablets should be swallowed whole, with a little water if necessary (but not with aerated mineral water).

Children under 15 years and Infants.

Dosage should be related to age within the range as follows:

0-3 years:	Usually 20-30 mg/kg/day.
3-15 years:	Dosage should range from 2 tablets to doses slightly less than those of adults.

All doses should be tailored to obtain optimum control and the treatment procedure should follow the same principle as in Adults.

CONTRA-INDICATIONS AND PRECAUTIONS

CONTRA-INDICATIONS

There are no specific contra-indications for Epilim but note should be taken of the following precautions.

PRECAUTIONS - GENERAL

No hepatic, renal, cardiac or haematological effects attributable to Epilim have been reported. At the start of treatment a few patients have experienced minor gastric irritation and less frequently, nausea. Should these symptoms persist they can be relieved by standard medication.

Combined Medication:
Epilim is well tolerated in combination with other anti-epileptic agents. Epilim may enhance the sedative effects of other agents, particularly barbiturates; this should be recognised when introducing Epilim to existing treatment and may require concomitant reduction in the dosage of other agents. Similarly Epilim, in common with many other medications, may potentiate the effect of mono-amine oxidase inhibitors (MAOI) and thymo-leptics and the doses of these agents should be reduced accordingly.

Diabetic Patients:
Epilim is partially eliminated by the renal route in the form of ketone bodies and this may give false positives when testing the urine of possible diabetics.

Overdosage:
Reports of accidental overdosage of Epilim have been rare. Recovery after the ingestion of up to 30g has been uneventful following conservative management.

As Epilim is absorbed very rapidly gastric lavage may be of limited value. However, as Epilim is excreted almost entirely within 24 hours (70% in the urine) it is recommended that general supportive measures be applied, paying particular attention to the maintenance of an adequate urinary output.

PRECAUTIONS - WOMEN OF CHILDBEARING AGE

In animals, this compound has demonstrated teratogenic properties in laboratory experiments. Any benefit from its use should be weighed against the possible hazard suggested by this finding.

Standard teratological studies suggest that other anticonvulsants such as phenytoin may have some adverse effect on foetal development. In view of this,care should be taken in prescribing all anticonvulsant compounds including Epilim to epileptic women who may become pregnant.

PRECAUTIONS - PHARMACEUTICAL

The tablets being hygroscopic must be kept in their protective foil until taken and should be stored in a cool dry place.

LEGAL CATEGORY

Prescription only medicine.

PACKAGE QUANTITIES

Carton containing 100 tablets in foil.

FURTHER INFORMATION

Epilim represents a new approach in the therapy of epilepsy. Whereas most of the currently available drugs have chemical features in common, Epilim is a different entity with a simple chemical structure which (unlike existing drugs) does not contain nitrogen. Biological studies on Epilim indicate that it may have a different mode of action in that it produces an increase in the level of γ -aminobutyric acid (GABA) in the brain by inhibiting GABA Transaminase which is responsible for the breakdown of GABA. Although there is no simple correlation between convulsive activity and GABA levels, evidence linking them is growing.

Clinically Epilim is effective in treatment of Petit Mal, Grand Mal, Mixed Epilepsies, and those with Temporal Lobe (or Psychomotor) components.

PRODUCT LICENCE HOLDER

Reckitt-Labaz

MANUFACTURERS

Reckitt & Colman Pharmaceutical Division,
Hull HU8 7DS

PRODUCT LICENCE NUMBER

0623/0001

DATA SHEET REFERENCE

This Data Sheet was printed in June 1974.

Further information is available on request from:
Reckitt & Colman Pharmaceutical Division
Hull HU8 7DS Tel: 0482 26151

Printed in Britain EP/1/74J

COMMITTEE ON SAFETY OF MEDICINES

Minutes of the meeting held on Thursday 28 March 1974

Present:

Sir Eric Scowen (Chairman)
Professor W I Cranston
Professor D G Evans
Dr D C Garratt
Professor R H Girdwood
Sir Austin Bradford Hill
Professor D R Laurence
Professor D V W Parke
Professor W Linford Rees
Professor J S Scott
Professor J B Stenlake

Dr E L Harris
(Acting Medical Assessor)
Mr S F Hall
(Pharmaceutical Assessor)
[redacted] (Secretary)

Also Present:

[redacted]) DHSS
) SHHD

Committee Secretariat

[redacted]

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1. Apologies for absence
2. Minutes of the meeting held on 28 February 1974
3. Matters arising from the minutes
4. Consideration of applications
5. The Medicines (Phenacetin Prohibition) Order
6. Notes for Guidance on Reproduction Studies
7. Herbal Remedies
8. Delays in Processing Applications
9. Committee's Annual Report - Revised Draft
10. Recommendations of the Sub-Committee on Adverse Reactions
    a. [redacted]
    b.
    c.
    d.
    e.
    f.
    g.
    h.
11. Medical Assessor's Report
12. Minutes of the Sub-Committees and matters arising

PL/0623/0001

Epilim

Sodium Valproate

(Anti-Convulsant)

Pharmacy Products Limited

Sub-Committee on Toxicity and Clinical Trials

The Sub-Committee considered a further report on the monitored release of epilim, sodium valproate, which had been submitted following the limited licence initially granted for this product. In view of the results presented, and in particular the further data on teratology the Sub-Committee now recommend as follows:

Recommendations

On the evidence before them the Sub-Committee recom variation of the product licence to delete the requirement regarding monitoring on condition that the indication for use reads as follows:

"for use in generalised, focal or other epilepsy bu only to be used in severe or resistant cases in women of child bearing age"

and that the following warning is included in all literature issued about this product;

"Women of Child Bearing Age"

This compound has been shown to be teratogenic in animals. Any benefit which may be expected from it use should be weighed against the hazard suggested by these findings".

Main Committee March 1974

On the evidence before them the Committee advise variation of the product licence to delete the requirement regarding monitoring condition that the indication for use reads follows:

"for use in generalised, focal or other epilepsy. In women of child bearing age, it should only be used in severe cases or those resistant to other treatment",

and that the following warning is included i all literature issued about this product;

"Women of Child Bearing Age

This compound has been shown to be teratogen in animals. Any benefit which may be expec ed from its use should be weighed against th hazard suggested by these findings".

The Committee noted that a special directive to designate this product as new was sent with the letter of intent when the original product licence was granted.

COMMITTEE ON SAFETY OF MEDICINES

Minutes of the Meeting held on Thursday 22 August 1974

Present:

Sir Eric Scowen (Chairman)
Dr D C Garratt
Professor R M Girdwood
Professor W Linford Rees
Dr M J Linnett
Professor W W Mushin
Professor D V W Parke
Professor J S Scott
Professor J B Stenlake
[redacted] (Medical Assessor)
[redacted] Pharmaceutical Assessor)
[redacted] (Secretary)

Also Present:

[redacted]) DHSS

Committee Secretariat

[redacted]

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1. Apologies for absence
2. Minutes of the meeting held on 25 July 1974
3. Matters arising from the minutes
4. Consideration of applications
5. Medical Assessor's Report
6. [redacted]
7. Anticonvulsants
8. Medicinal Products on Prescription Only
9. [redacted]
10. [redacted]
11. Minutes of the Sub-Committees
12. Progress of Applications
13. Items for information
14. Date and time of next meeting

APPENDICES

A. Consideration of Individual Applications
B. Advice given on minor applications
C. Written Representations:
(i) [redacted]
(ii)
(iii)
(iv)
(v)

[redacted]

7. EPILIM - (SODIUM VALPROATE - PAPER 3 (APPLICATION PL/0623/0001))

7.1 The paper before the Committee recalled that in March they had considered a request to vary this product licence to remove the monitored release requirement restricting promotion to epileptic centres and to allow Epilim, a new anti-convulsant, to be generally promoted. They had then recommended that the variation could be allowed on condition that:-

a) the indication for use read as follows:

"For use in generalised, focal or other epilepsy. In women of child-bearing age it should only be used for severe cases or those resistant to other treatment" and

b) that the following warning was included in all literature issued about the product:

"Women of child-bearing age
This compound has been shown to be teratogenic in animals. Any benefit which may be expected from its use should be weighed against the hazards suggested by these findings."

Before proceeding with the variation, officials had sought the views of the Minister of State (Health) in view of the concern regarding the availability of drugs which could harm the foetus. On the understanding th on the basis of animal studies, the teratogenic effects of Epilim were of the same order as phenytoin, the Minister agreed to the variation.

7.2 The Committee advised that all literature, eg data sheets, journal adverti representative hand-outs and medical mailings must contain the warning.

8. ANTI-CONVULSANTS IN PREGNANCY - PAPER 5

The Committee agreed to a suggestion that the views of the Sub-Committee on Adver Reactions should be sought on the question of whether a further general warning should be given to doctors about the possible dangers associated with the administration of anti-convulsants to pregnant women.

The Committee were pleased to note that licence-holders of anti-convulsant preparations containing phenytoin and phenobarbitone which were actively promoted had been asked to insert a warning in their data sheets, if not already included, in the following terms

"There is some evidence that anti-convulsant medicines can cause foetal abnormalities and care is needed in their use during the early months of pregnancy. The physician must consider the relative hazards to both mother and foetus associated with the withdrawal or reduction of anti-convulsant therapy and of continuing therapy with the possibility of inducing congenital malformations."

9. MEDICINAL PRODUCTS ON PRESCRIPTION ONLY - PAPER 4

10.

11.

12. MINUTES OF THE SUB-COMMITTEES

The Committee received for information the unconfirmed minutes of the Joint Sub-Committee on Anti-microbial Substances - Meeting 30 July 1974.

13 PROGRESS OF APPLICATIONS

The Committee received the following:

PRO 1 Schedule of applications subject to outstanding Section 21(1) or Schedule 2(2) procedures

PRO 2 Status Summary of Section 21(1) or Schedule 2(2) cases

PRO 3 Status Summary on applications - July 1974

PRO 4 Schedule of Product Licences and Clinical Trial Certificate - July 1974

PRO 5 List of deferred Applications

NOT FOR PUBLICATION CSM/74 - 9th Meeting

COMMITTEE ON SAFETY OF MEDICINES

Minutes of the Meeting held on Thursday 26 September 1974

Present:

Sir Eric Scowen (Chairman)
Professor W I Cranston
Sir Theo Crawford
Professor D G Evans
Dr D C Garratt
Sir Austin Bradford Hill
Professor W Linford Rees
Dr M J Linnett
Professor T E Oppé
Professor D V W Parke
Professor J S Scott

Dr E L Harris (Medical Assessor)
Mr S F Hall (Pharmaceutical Assessor)
[redacted] (Secretary)

Also Present:

[redacted] DHSS

[redacted] Director, Bureau of Drugs, Canadian Health and Welfare Depart

Committee Secretariat

[redacted]

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1. Apologies for absence
2. Minutes of the meeting held on 22 August 1974
3. Matters arising from the minutes
4. Consideration of applications
5. Medical Assessor's report
6. [redacted]
7. Licensing of products containing herbal ingredients
8. Review of Product Licences
9. Membership of the Sub-Committee on Toxicity, Clinical Trials and Therapeutic Efficacy
10. Recommendations from the Sub-Committee on Adverse Reactions
11. Minutes of the Sub-Committees
12. Progress of Applications
13. Items for Information
14. Date and time of next meeting

[redacted]

3.2 Epilim (Sodium Valproate) - (Application PL 0623/0001)
(Minute 7 of CSM/74 - 8th Meeting)

Dr Harris reported that the conditions which the Committee had advised should be imposed were acceptable to the applicant.

4. Consideration of Applications

4.1 At the start of the meeting, the Committee held a hearing and considered written representations relating to the following applications:

[redacted]

5. Medical Assessor's Report

Dr Harris reported that the processing of applications had continued satisfactorily.

6. [redacted]

NOT FOR PUBLICATION

CSM/80/11th Meeting

COMMITTEE ON SAFETY OF MEDICINES

Minutes of the meeting held on Thursday 30 October 1980

Present

Professor A Goldberg (Chairman)
Professor M Rawlins
Dr J Smith
Professor F A Jenner
Dr F Fish
Dr M Richards
Professor B M Hibbard
Professor P H Elworthy
Professor W I Cranston
Professor D G Grahame-Smith
Professor J Lloyd
Dr J Holt
Professor R H Girdwood
Professor D V W Parke
[redacted] (Secretary)
Dr G Jones (Medical Assessor)
Dr J Calderwood (Pharmaceutical Assessor)

Committee Secretariat

[redacted]

Also present

[redacted]

1. ANNOUNCEMENTS

1.1 The Chairman reminded members that the information before them, and the proceedings, were confidential and should not be disclosed.

2. [redacted]

e) Sodium Valproate

i) The Committee considered a proposal from the Licensing Authority(based on the recommendation from the Sub-Committee on Adverse Reactions) that the data sheet(s) and, if necessary, the product licence(s) of products containing sodium valproate should be varied under Section 28(1) and Schedule 2 of the Medicines Act 1968, on grounds of safety, to include the following statements

"Red cell hypoplasia and leucopenia have been reported with sodium valproate. In cases where the drug was discontinued, the blood picture returned to normal".

"Sodium valproate may produce metabolic upset by interference with propionic acid metabolism, causing secondary hyperammonaemia. This may manifest clinically as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur sodium valproate should be discontinued".

ii) The Committee accepted the proposal of the Licensing Authority but agreed that, in the first instance, it would not be necessary to exercise the powers of Section 28(1) or Schedule 2 of the Act since there was a possibility that the variation, as detailed above, could be agreed informally with the company(s) concerned.

iii) It was noted that the products involved were Epilim tablets and syrup.

iv) It was further agreed that attention should be drawn to the warnings in a future issue of Current Problems.

f) [redacted]

7. WRITTEN REPRESENTATION

[redacted]

8. HEARINGS

[redacted]

9. SECRETARY AND MEDICAL ASSESSOR'S ORAL REPORT

There was none.

COMMERCIAL IN CONFIDENCE

CSM/82/11th Meeting

COMMITTEE ON SAFETY OF MEDICINES

Minutes of the meeting held on Thursday 18th November 1982

Present

Professor A Goldberg (Chairman)
Professor D G Grahame-Smith
Professor M D Rawlins
Professor P H Elworthy
Professor W I Cranston
Professor H K Weinbren
Dr J Smith (a)
Dr M Richards
Professor J Crooks
Mr W Darling
Professor R H Girdwood
Dr J M Holt
Professor F A Jenner
Professor J Dundee
Professor B M Hibbard
Professor M P Vessey
Dr F Fish
Professor Hull

(a) am only

Committee Secretariat

[redacted]

Also present

[redacted]

A Goldberg 16/12/82

1. APOLOGIES AND ANNOUNCEMENTS

1.1 The Chairman reminded members that the papers and the proceedings were confidential and should not be disclosed.

1.2 Apologies for absence were received from Professor Read.

2. MINUTES OF THE MEETING HELD ON 20 AND 21 OCTOBER 1982.

The minutes were agreed and signed as a true record with the following amendments;

[redacted]

Hearing 3.

[redacted]

3. MATTERS ARISING FROM THE MINUTES

None.

[redacted]

PAPER TWO SODIUM VALPROATE AND NEURAL TUBE DEFECTS.

The Committee noted that there were tabled additions to this Paper and that a paper on Sodium Valproate and Congenital Malformation had also been tabled. The Committee requested that the papers be amalgamated and submitted for consideration at the next meeting.

COMMERCIAL IN CONFIDENCE

COMMITTEE ON SAFETY OF MEDICINES

Minutes of the meeting held on Thursday 16 December 1982

Present

Professor A Goldberg (Chairman)
Professor D G Grahame-Smith
Professor M D Rawlins
Professor W I Cranston
Professor H K Weinbren
Dr J Smith
Dr M Richards
Professor J Crooks
Mr W Darling
Professor R H Girdwood
Dr J M Holt
Professor F A Jenner
Professor J Dundee
Professor B M Hibbard
Dr Fish
Professor D Hull
Professor Elworthy

Committee Secretariat

[redacted]

Also present

[redacted]

1. APOLOGIES AND ANNOUNCEMENTS

1.1 The Chairman reminded members that the papers and the proceedings were confidential and should not be disclosed.

1.2 Apologies for absence were received from Professor Vessey.

[redacted]

2. MINUTES OF THE MEETING HELD ON 18 NOVEMBER 1982

The minutes were agreed and signed as a true record with the following amendment:

[redacted]

[redacted]

3.2 [redacted]

3.3 [redacted]

3.4 PAPER 4 - SODIUM VALPROATE AND TERATOGENICITY

3.4.1 The Committee considered this Paper which had been considered by the SEAR Sub-Committee and also a tabled paper on the same subject. These two Papers included reports on Teratogenicity in France, various articles in the professional and non-professional press and Data received from the Company concerning the offspring of pregnant women who had received Epilim.

3.4.2 The Committee agreed with the licensing authority view that no formal action was required against the product licences.

3.4.3 Although the current warning in the Data Sheet was adequate the Committee would not object to the amendment proposed by the Company along the lines that pregnancy should be carefully monitored in women receiving Epilim.

3.4.4 The Committee concurred with the SEAR recommendation that there was a need for specific research into the role of anti-convulsant therapy in epileptic mothers in increasing the risks of congenital malformation of the foetus.

3.4.5 The Committee agreed that an item on this topic should be included in Current Problems and that it should be issued as soon as possible. Instead of the normal procedure for approving Current Problems, the Committee agreed that the draft of the item was to be agreed by the Chairman of the main Committee, the Chairman of the Editorial Board and the Chairman of the SEAR Sub-Committee. The draft would be approved by the remainder of the main Committee by correspondence.

COMMITTEE ON SAFETY OF MEDICINES

CURRENT PROBLEMS

NUMBER

9

JANUARY
1983

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Sodium Valproate (Epilim) and congenital abnormalities

INTRODUCTION

The Current Problems series is intended to draw attention to matters of particular concern or interest which have been considered by the CSM. It also indicates some of the topics about which reports will be especially valuable.

It is hoped that Current Problems will facilitate the flow of information to and from the Committee. The CSM always welcomes reports where adverse effects are suspected, particularly when they are clinically serious, unexpected, or when new medicinal products are involved.

SODIUM VALPROATE (EPILIM) AND CONGENITAL ABNORMALITIES

Over the past fifteen years there have been a number of epidemiological surveys in various parts of the world reporting an increase in the incidence of congenital malformations in the children born to women with epilepsy,[1,2,3,4] although it is difficult to determine whether it is the disease itself or the medication used in its treatment which is responsible for the increased malformation rate. In most of the surveys, the incidence of malformations has been higher in epileptics receiving drug treatment during pregnancy than in those untreated.[5,6] Although the major structural abnormalities are induced in early pregnancy there is some evidence that treatment in later pregnancy also affects development.[5,7,8] Folic acid deficiency may be important since many anticonvulsant drugs lower serum folate levels, and altered folate metabolism could be responsible for some of the malformations observed.

Almost all surveys show a two- to three-fold increase in the incidence of congenital anomalies among babies born to epileptic women. The most frequently occurring defects, in 2285 children exposed to anticonvulsant therapy in utero[6] were cleft lip with or without cleft palate (3.0%), skeletal anomalies (1.9%), congenital heart disease (1.4%), CNS defects (1.2%), anomalies of the gastro-intestinal tract (1.1%), facial and ear abnormalities (1.0%), mental retardation (0.7%), genito-urinary anomalies (0.6%). Other isolated anomalies occurred. The risk to a woman with epilepsy, who is receiving an anticonvulsant, of delivering a malformed child is thus about one in ten.[9] Nevertheless, withdrawal of anticonvulsants is not generally advisable because fetal hypoxia due to maternal fits is likely to be at least as damaging as the drugs themselves.[10]

Recent reports have drawn attention to valproate and its apparent association with neural tube defects in babies born to women with epilepsy treated with it during pregnancy. Valproate, like other anticonvulsants, is known to be teratogenic in animals and one report suggests that it may also be teratogenic in humans.[11] The malformations reported to occur with valproate are similar to those with other anticonvulsants, namely neural tube defects, congenital heart lesions, digital anomalies and oral clefts. The recent recommendations[12,13] that "newer" drugs such as valproate may be the drugs of choice for treating epileptic women cannot be accepted uncritically. A new drug may only appear less hazardous because evidence of hazard has not accumulated.

There is no clear evidence that any one anticonvulsant drug is safer or more dangerous than any other. Anticonvulsant therapy should be reviewed in any epileptic woman who is pregnant, or contemplating pregnancy, so that the simplest effective regimen can be implemented. There may be a case for withdrawing treatment during pregnancy in suitable patients with minor epilepsy where consciousness is not lost during attacks. In general, it is preferable to use single drug therapy in women of reproductive potential. Established folate deficiency should certainly be remedied, though the precise role of altered folate metabolism is in doubt. Maternal serum alphafetoprotein, high resolution ultrasound scanning and even diagnostic amniocentesis are available, if indicated, to assist with counselling.

References:

1. Elshove J and van Eck J H M (1971) Congenital malformations particularly cleft lip with or without cleft palate in children of epileptic mothers. Ned Tijdsch Geneesk 115, 1371.
2. Meadow S R (1970) Congenital abnormalities and anticonvulsant drugs. Proc Roy Soc Med 63, 48-9.
3. Fedrick J (1973) Epilepsy and pregnancy. A report from the Oxford Record Linkage Study. Br Med J 2, 442-8.
4. Sullivan F M (1979) The teratogenic and other toxic effects of drugs on reproduction in Iatrogenic Diseases edited by D'Arcy P F and Griffin J P, Second Edition, 445-7.
5. Speidel B D and Meadow S R (1972) Maternal epilepsy and abnormalities of the foetus and newborn. Lancet 2, 839-43.
6. Hill R M (1973a) Teratogenesis and antiepileptic drugs. New Engl J Med 289, 1089-90.
7. Hill R M (1973b) Drugs ingested by pregnant women. Clin Pharmacol Ther 14, 654-9.
8. Hiilesmaa V K et al (1981) Fetal growth retardation associated with maternal anti-epileptic drugs. Lancet 2, 165-167.
9. Speidel B D and Meadow S R (1974) Epilepsy, anticonvulsants and congenital malformations. Drugs 8, 354-65.
10. Lowe C R (1973) Congenital malformations among infants born to epileptic women. Lancet 1, 9-10.
11. Bjerkedal T et al (1982) Valproic Acid and Spina Bifida. Lancet 2, 1096.
12. Leading Article (1981) Teratogenic risks of anti-epileptic drugs. Br Med J 2, 515-6.
13. McEwan H P (1982) Drugs in pregnancy. Prescribing. Br J Hosp Med 28:6, 559-65.

Issued by: Committee on Safety of Medicines, Market Towers, 1 Nine Elms Lane, London, SW8 5NQ

Printed in England for HMSO Dd8329042 155m 1/83

COMMITTEE ON SAFETY OF MEDICINES

CURRENT PROBLEMS in Pharmacovigilance

MEDICINES CONTROL AGENCY

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Ketorolac: new restrictions on dose and duration of treatment

Serious and fatal adverse reactions have been associated with the use of ketorolac. The recommended dose and duration of treatment have been reduced.

Ketorolac (Toradol▼) is a non-steroidal anti-inflammatory agent licensed for short-term management of moderate to severe acute post-operative pain. The product was first launched in the USA in 1990 and has been available in the UK since October 1991.

By December 1992, about 16 million patients worldwide had received all formulations of ketorolac including 9.3 million patients in the USA and Canada. In total there had been 923 spontaneous reports of serious reactions with ketorolac. More than 90% of these reports originated from the USA. The majority of reported reactions are those recognised for NSAIDs and include gastrointestinal (203), haematological (181), renal (124), hypersensitivity (102) and neurological reactions (111).

World-wide, there have been 97 reported reactions with a fatal outcome to date. The causes of death are shown in the following table. Other factors occurring in the post-operative period are likely to have contributed and a causal association between ketorolac and death is difficult to confirm.

Cause of death	No. of cases
Gastrointestinal bleeding/perforation	47
Renal impairment/insufficiency	20
Anaphylaxis/asthma	7
Haemorrhagic reactions	4
Unexplained death	6
Miscellaneous causes	13

In the UK it is estimated that 190,000 patients have received ketorolac. We have received 59 reports (1 fatal) describing 91 reactions associated with the drug. The most commonly reported individual reactions include bronchospasm (6), post-operative haemorrhage (5), gastrointestinal haemorrhage (4, 1 fatal), anaphylactic reactions/allergy (3) and convulsions (2).

Information is also available from an interim analysis of a US cohort study comparing post-operative use of ketorolac and opioid analgesia. This study and other data indicate that the following factors are associated with an increased risk of gastrointestinal bleeding with ketorolac:

- Age > 65 years
- A history of peptic ulceration
- Concomitant treatment with anti-coagulants and other NSAIDs
- Dose of ketorolac
- Duration of treatment with parenteral ketorolac in excess of 2 days.

The following changes in the recommended dose and duration of treatment have been made:

Dose

- Parenteral administration: the starting dose has been reduced to 10 mg with subsequent doses of 10-30 mg four to six hourly as required. The total daily dose has been reduced to 90 mg for the non-elderly and 60 mg for the elderly. The lowest effective dose should be given.
- The oral dosage recommendations remain unchanged.

Duration

- The maximum duration of parenteral treatment has been reduced to two days for all age groups.

Contra-indications

Doctors are particularly reminded that ketorolac should **not** be used in patients with:

- A history of peptic ulceration or gastrointestinal bleeding
- A history of haemorrhagic diathesis
- A history of confirmed or suspected cerebro-vascular bleeding
- Operations associated with a high risk of haemorrhage
- A history of asthma
- Moderate or severe renal impairment (serum creatinine > 160 μmol/l)
- Hypovolaemia or dehydration from any cause
- Hypersensitivity to NSAIDs or aspirin

Furthermore, ketorolac should not be used during pregnancy or lactation, or concomitantly with the following drugs:

- Other NSAIDs
- Anticoagulants (including low dose heparin)

The safety of ketorolac is being monitored closely and the need for any additional measures will be reviewed when further data are available.

Sulphasalazine and fatal blood dyscrasias

Sulphasalazine should be stopped immediately there is suspicion of a blood dyscrasia.

Blood disorders constitute 19% of all reactions reported with sulphasalazine (Salazopyrin) and include 191 reports of neutropenia, leucopenia or agranulocytosis (22 fatal), 44 reports of bone-marrow depression or aplastic anaemia (13 fatal) and 30 reports of thrombocytopenia (1 fatal). The 36 fatal cases included 22 females and 13 males with a mean age of 57 years (10-84). Twenty-three patients had been treated for inflammatory bowel disease and 9 for rheumatoid arthritis. The reaction was reported to have occurred within 3 months of starting sulphasalazine in 14 patients, from 3 to 6 months in 6 patients and from 6 to 11 months in a further 2 patients.

In the literature, leucopenia has been reported to occur in up to 1.5%[1] and agranulocytosis at a peak incidence of 1 in 700 patients during the second month of therapy[2].

Patients should be asked to report to their doctors immediately with any unexplained fever, sore throat, malaise or other non-specific illness.

It is recommended that blood counts are performed before treatment and monthly for the first three months of therapy. Sulphasalazine should be stopped immediately there is suspicion of a blood dyscrasia. The potential of 5-amino-salicylate to cause blood dyscrasias is currently unclear.

1. Amos RS *et al.* Br. Med. J. 1986; 293: 420-423.
2. Keisu M and Ekman E. Eur. J. Clin. Pharmacol. 1992; 43: 215-218.

What does this symbol mean?

- The product contains a new drug
- All suspected ADRs should be reported

Was the drug responsible?

Determining cause and effect

Deciding whether or not a drug is responsible for a particular adverse occurrence is a matter of clinical judgement. Few adverse drug reactions are unique syndromes and therefore a number of factors need to be taken into account.

(1) Nature of the reaction

Some clinical events are quite likely to be drug-related and their occurrence should immediately prompt consideration of a possible drug cause. Examples of these are some skin reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis), blood dyscrasias and acute dystonias.

(2) Timing

The interval between beginning treatment and developing a reaction may be characteristic of the reaction. For example, anaphylaxis usually occurs within a few minutes of parenteral drug administration. Alternatively, some reactions develop months or years later and might be related to a cumulative effect of the drug or even an effect on the next generation, e.g. diethylstilboestrol and vaginal cancer.

(3) Relationship to dose or drug withdrawal

Adverse reactions are often dose-related and may be avoidable by using a reduced dose. Many reactions will resolve on stopping the drug; this supports cause and effect but could be coincidental.

(4) Re-challenge

Recurrence of an adverse effect on re-challenge with a suspected drug is strongly suggestive that the drug was responsible, especially when it is accompanied by objective evidence. However, following serious reactions, deliberate re-challenge is seldom justifiable.

(5) Exclusion of other possible causes

An adverse drug reaction is often one of a number of possible diagnoses. The clinical picture may be a manifestation of the underlying illness or another disease. Often there is more than one drug which could have been responsible or an interaction between two drugs needs to be considered. For some reactions, specific investigations such as plasma drug concentrations and immunological or histopathological studies may be of diagnostic value, e.g. liver biopsy for drug-induced hepatitis.

(6) Is the reaction recognised?

Well-recognised reactions are mentioned in the British National Formulary and the product data sheet. Otherwise, information may be available from regional or hospital drug information centres or via the CSM Freephone. Irrespective of whether a reaction has previously been recognised as associated with the suspected drug it is always necessary to evaluate whether the factors discussed above support cause and effect.

(7) Reporting adverse reactions

It is particularly important to report reactions which have not been recognised previously but are clinically plausible. One of the main purposes of the yellow card scheme is to identify hitherto unrecognised reactions. **Please do not be deterred by uncertainty regarding cause and effect.**

Reporting reactions to biotechnology products

Use approved or brand names to report reactions to biotechnology products

In recent years various "biotechnology" products have become available as medicines. They are produced using cell culture techniques and gene expression. Examples include human insulins, growth hormones, erythropoietins, recombinant tissue plasminogen activators (e.g. alteplase), growth factors (e.g. filgrastim and molgramostim), interferons and vaccines. These products usually closely resemble their naturally occurring counterpart, but are rarely identical. They may have a slightly different amino-acid sequence, or different glycosylation.

Unfortunately, doctors reporting suspected reactions sometimes use a non-specific name for the drug on the yellow card. For example if a reaction to "erythropoietin" is reported, it will not be clear to us whether epoetin alpha (Eprex) or epoetin beta (Recormon) was implicated. As more biotechnology medicines become available it will be increasingly difficult to identify the product unless an approved or brand name is used.

REMINDERS

Avoid all NSAIDs in aspirin-sensitive patients

- Aspirin may provoke or exacerbate asthma in up to 5% of asthmatics. "Cross-sensitivity" can occur between aspirin and other NSAIDs.
- We have received a report of a young patient who died from acute asthma 4 hours after a single 25 mg dose of diclofenac. The patient was known to be sensitive to aspirin.
- The use of NSAIDs is contraindicated in patients with a known history of hypersensitivity to aspirin.
- NSAIDs are also a potential hazard to patients with asthma.

Report serious adverse reactions to non-prescription medicines

- An increasing number of medicines are being made available for sale from pharmacies without prescription.
- Safety is the principal criterion used to decide whether a medicine may be made available without prescription.
- Nevertheless, unforeseen safety hazards may still arise with over-the-counter medicines.
- Serious adverse reactions arising from patient-initiated treatment should be reported to us in the usual way.

Neural tube defects associated with sodium valproate and carbamazepine - need for counselling and screening

- The use of sodium valproate or carbamazepine in early pregnancy is associated with an increased risk of neural tube defects.
- Women taking these drugs who may become pregnant should be informed of the possible consequences.
- Those who wish to become pregnant should be referred to an appropriate specialist for advice.
- Women who do become pregnant should be counselled and offered ante-natal screening (alpha-fetoprotein measurement and a second trimester ultrasound scan).

Neuropsychiatric adverse reactions associated with fenfluramines

- Dexfenfluramine (Adifax▼) and DL-fenfluramine (Ponderax) are indicated as **adjuncts to diet** for the treatment of **severe** obesity. They should be used for a **maximum of 3 months.**
- Serious neuropsychiatric reactions reported in association with fenfluramines include hallucinations and depression.
- Treatment with these drugs should be avoided in patients with a history of psychiatric illness.

Current Problems in Pharmacovigilance is produced by the Committee on Safety of Medicines and the Medicines Control Agency.

Editorial Board: Professor M.D. Rawlins, Professor M.J.S. Langman, Dr S.M. Wood, Dr P.C. Waller and Dr M.L.A. Crawford (secretary).

Enquiries, comments and suggestions to Dr M.L.A. Crawford, Medicines Control Agency, Room 1023, Market Towers, 1, Nine Elms Lane, London SW8 5NQ.

Doctors and dentists should notify a change of address by writing to the Medical Direct Mail Organisation Ltd, Hazleton Industrial Park, Lakesmere Road, Horndean, Waterlooville, Hampshire, PO8 9JU, or by dialling the Hotline number 0705 571354. Addresses supplied in connection with mailings on behalf of CSM and MCA will not be used for other mailings without the permission of the doctor concerned. **Pharmacists in Great Britain and Northern Ireland** do not need to communicate a change of address provided that this has already been notified to the Pharmaceutical Society with whom they are registered.

RESTRICTED – COMMERCIAL **CSM/WGPM/2002/3rd Meeting**

NOT FOR PUBLICATION

COMMITTEE ON SAFETY OF MEDICINES

WORKING GROUP ON PAEDIATRIC MEDICINES

MINUTES OF THE MEETING HELD ON WEDNESDAY 27 NOVEMBER 2002 AT 11 a m IN THE 19th FLOOR CONFERENCE ROOM, MARKET TOWERS

Members Present
Professor R L Smyth (Chair)
Professor A Aynsley- Green
Dr T L Chambers
Professor M Kendall
Dr S Logan
* Dr R MacFaul
Mr T Nunn
Dr G Rylance
Professor T Stephenson

MCA Officials Present Supporting Specific Items
[redacted]

Others
[redacted]

Apologies
Professor J Collier
Professor K Park
Dr S Watkins

Members for the Day
Dr Amin R Hodjegan
Dr G Meakin
Dr P Meredith
Professor G Tucker

Observer
Professor A M Breckenridge

Secretary
[redacted]

* Not present for items 4, 5 & 6

1. Announcements/apologies

1.1 The Chairman welcomed and reminded members that the papers and proceedings of the Working Group (WG) were confidential and should not be disclosed. Members were also asked to declare any personal or non-personal interests in relation to Agenda items.

[redacted]

AFTERNOON SESSION 1.30pm

7. [redacted]

8. **Sodium valproate and developmental delay**

The Working Group reviewed the paper 'Sodium valproate in pregnancy and risk of developmental delay.' This was an update of a previous paper on this issue reviewed in November 2000. The WG considered that there was now evidence from a number of studies suggesting an increased risk of developmental delay following in-utero exposure to sodium valproate. The WG advised that product information should be updated to include a warning of this possible risk. The proposed SPC wording was endorsed with some minor amendments. The WG advised that there was a need to communicate this information. An article in Current Problems in Pharmacovigilance was the preferred method but should not be unduly delayed awaiting final publication of papers. Use could be made of the CSM website as appropriate.

COMMITTEE ON SAFETY OF MEDICINES

CURRENT PROBLEMS in Pharmacovigilance

MHRA
Medicines and Healthcare products Regulatory Agency
Safeguarding public health

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A tear-off factsheet on SSRIs is attached at the back of this edition

Internet version: http://medicines.mhra.gov.uk/ourwork/monitorsafequalmed/currentproblems/currentproblems.htm

HRT : Update on the risk of breast cancer and long-term safety

In October 2002, we updated you on the long-term safety of HRT following publication of the preliminary results of the USA's Women's Health Initiative (WHI) randomised controlled trial[1].

The recent publication of the findings of the UK's Million Women Study[2] and the final results of the WHI trial[3] provide important new evidence with respect to the risk of breast cancer with HRT.

The Committee on Safety of Medicines (CSM) and its expert working group (EWG) on HRT have kept the safety of HRT under careful review as new data have become available. Recent publication of two high quality studies[2,3] has prompted the CSM and its EWG to re-examine the risk of breast cancer in association with HRT use.

These studies have confirmed that use of oestrogen-only therapy is associated with a small increase in the risk of breast cancer (relative risk [RR] = 1.30). They have also shown that the increase in risk of breast cancer in users of combined (oestrogen plus progestogen – both continuous and sequential regimens) HRT (RR = 2.00), is substantially higher than in users of oestrogen-only HRT.

In addition, tibolone (Livial▼), a steroid that possesses oestrogenic, progestogenic and androgenic activity and has the same licensed indications as conventional HRT, was shown to significantly increase the risk of breast cancer, though to a lesser extent than combined HRT.

Having reviewed the latest results, CSM has advised that each decision to start HRT should be made on a case-by-case basis and treatment should be regularly reappraised (at least once per year).

The new studies

The Million Women Study was a large observational study that examined the effects of different types of HRT, including tibolone, on the incidence of breast cancer in nearly a million postmenopausal women in the UK over a 5 year period. The National Health Service Breast Screening Programme, which invites all women in the UK aged between 50 and 64 years for routine screening once every 3 years, was used to recruit women.

The WHI, a randomised, placebo-controlled trial in the USA examined the breast cancer risk of long-term treatment with one specific combined HRT preparation (containing 0.625mg conjugated equine oestrogens and 2.5mg medroxyprogesterone acetate) in over 16,500 women for an average of 5.2 years.

Key findings

These studies confirm that all types of HRT cause a duration-dependent increase in the risk of breast cancer that begins to decline when HRT is stopped and, by 5years, reaches the same level as in women who have never taken HRT.

For oestrogen-only products the previously described small increase in risk of breast cancer is confirmed but for combined HRT the increased risk is substantially higher than previously thought.

More specifically, these studies show that:

- The increase in risk of breast cancer associated with combined HRT (RR = 2.00 compared with no use) is significantly higher than for oestrogen-only therapy (RR = 1.30).
- The increase in risk becomes apparent within 1-2 years of starting treatment, irrespective of the type of HRT used.
- There is no evidence for a difference in risk of breast cancer between specific preparations or their route of administration within the classes of oestrogen-only therapy or combined HRT.
- Tibolone also significantly increases the risk of breast cancer compared with no HRT use (RR = 1.45)

The findings of the WHI trial casts doubt on the previous observation that the tumours diagnosed in HRT users were less likely to have spread beyond the breast than in non-users. However, further evidence is required to confirm this.

In view of these findings, it is important for all women, including those taking HRT or tibolone, to be 'breast aware' and to accept invitations for breast screening from the age of 50 (www.cancerscreening.nhs.uk/ breastscreen/ breast awareness.html).

Implications for prescribing

- The results of the Million Women Study do not necessitate any urgent changes to women's treatment.
- For short-term use of HRT for the relief of menopausal symptoms, the benefits are considered to outweigh the risks for many women.
- For longer-term use of HRT, women must be made aware of the increased incidence of breast cancer and other adverse effects (see table 1 overleaf).
- Each decision to start HRT should be made on an *individual* basis, and treatment should be regularly reappraised (at least once a year).

Deciding about the type of HRT preparation

Oestrogen-only HRT is associated with a clinically significant increase in the risk of endometrial disorders, including cancer.

For combined HRT the benefits of the lower risk of endometrial disorders, including cancer, should be weighed against the new information about the increased risk of breast cancer (see table 1 overleaf).

The risk of endometrial cancer with tibolone is not known.

- For women without a uterus: Oestrogen-only therapy is appropriate.
- For women with a uterus: This will be a difficult decision for women and their doctors to make. Women must be made aware of the increased incidence of breast cancer and other adverse effects (see table 1 overleaf).

Long-term safety of HRT

Table 1 provides an updated summary of the risks and benefits of long-term HRT use. Prescribers are reminded that while incidences have been calculated for 5 and 10 year periods, in the Million Women Study and the WHI trial, the increase in breast cancer risk started to become apparent within 1-2 years of initiating HRT treatment.

1. MHRA/CSM Current Problems in Pharmacovigilance. 2002; 28: 1-2
2. Lancet 2003; 362: 419-427
3. Chlebowski RT et al. JAMA 2003; 289(24):3243-3253
4. S Evans. Manuscript in preparation.
5. Beral V et al. Lancet 2002; 360: 942-944 (based on Writing Group for the Women's Health Initiative Investigators. JAMA 2002; 288(3): 321-333)

Table 1 Summary of the risks and benefits associated with using HRT.

Condition	Age of woman (yr)	Number of cases per 1000 non-HRT users	Extra number of cases in 1000 HRT users over the same period	
Cumulative cancer risk over 15 or 20 years			**5 years use**	**10 years use**
Breast cancer	50-65	32	1.5 (±1.5) oestrogen-only 6 (±1) (combined HRT)	5 (±2) oestrogen-only 19 (±1) (combined HRT)
Endometrial cancer	50-64	5	4 (oestrogen-only) Data not available for combined HRT	10 (oestrogen-only) ≤2* (combined HRT)
Ovarian cancer[b]	50-69	9	1 (±1) (oestrogen-only)	3 (±2) (oestrogen-only)
Cardiovascular risks over 5 years				
Stroke	50-59 60-69	3 11	1 (±1) 4 (±3)	Data not available
VTE	50-59 60-69	3 8	4 (±2) 9 (±5)	Data not available
Benefits over 5 years			**Reduced number of cases in 1000 HRT users over the same period**	
Colorectal cancer	50-59 60-69	3 8	1 (±1) 3 (±2)	2 (±2) 5-6 (±4)
Fracture of neck of femur	50-59 60-69	1-2 7-8	0-1 (±1) 2-3 (±2)	1 (±1) 5 (±3)

Numbers are best estimates (± approximate range from 95% Confidence Intervals).
* There may be a difference in the risk of endometrial cancer between sequential and continuous combined HRT.
Sources of data: breast cancer[2]; ovarian cancer[4]; stroke and VTE[5]
[b] The risks of ovarian cancer with combined HRT are not known

Topical vaginal oestrogens: endometrial safety

As part of their ongoing review of the safety of HRT, the CSM has recently considered the endometrial safety of topical vaginal oestrogens.

Prescribers should note that:

- Although the usage of these preparations is largely short-term, they are often used repeatedly by patients on an *ad hoc* basis, when symptoms recur.
- The risk of endometrial hyperplasia and carcinoma is increased when *systemic* oestrogens are administered unopposed for prolonged periods of time.
- The systemic availability of topical vaginal oestrogens is largely unknown but most are used without added progestogen.
- The endometrial safety of long-term/repeated use of topical vaginal oestrogens is uncertain.

In view of this, prescribers are reminded that, in women with an intact uterus:

- Topical oestrogens should be used in the lowest effective amount to minimise systemic absorption.
- Treatment should be interrupted at least annually to re-assess the need for continued treatment.
- If break-through bleeding or spotting appears at any time on therapy, the reason should be investigated and may include endometrial biopsy to exclude endometrial malignancy.

SSRI and venlafaxine use in children

This article summarises the licensed indications of Selective Serotonin Reuptake Inhibitors (SSRIs) and venlafaxine a Serotonin Noradrenaline Reuptake Inhibitor (SNRI) in children and adolescents.

Paroxetine (Seroxat): safety in children and adolescents

Contraindicated in under 18s with depressive illness

Paroxetine is not licensed for use in those under 18 but it has been used in this age group outside its licensed indications.

New data from clinical trials of paroxetine (Seroxat) in children and adolescents do not demonstrate efficacy in depressive illness in this age group and show an increase in the risk of adverse events including self harm and potentially suicidal behaviour in the paroxetine group compared to placebo. Various analyses suggest that the risk of these adverse events is between 1.5 and 3.2 times greater with paroxetine compared to placebo.

On the basis of these data, the CSM considers that the balance of risks and benefits of paroxetine is unfavourable when used to treat depressive illness in this age group.

Prescribing advice

- Paroxetine should not be prescribed as new therapy for patients under 18 years of age with depressive illness.
- For patients being successfully treated with paroxetine, then the completion of the planned treatment course should be considered as an option in the management of the illness.
- For patients not responding to or suffering adverse effects on paroxetine, a change of treatment is recommended.

Other SSRIs and venlafaxine in children

Paediatric safety and efficacy cannot be extrapolated from experience in adults

Depressive disorders

No SSRI/SNRI is licensed in the UK for the treatment of depression in children and adolescents aged <18 years.

Venlafaxine (Efexor) is contraindicated in children and adolescents aged <18 years.

In clinical trials, sertraline (Lustral) has not been shown to be effective in paediatric depression or panic disorder. Citalopram (Cipramil), escitalopram (Cipralex), fluvoxamine (Faverin) and fluoxetine (Prozac) are **not licensed** for depression in children. However, fluoxetine is licensed for the treatment of depression in children aged 8 years and above in the USA.

Anxiety Disorders including obsessive compulsive disorder (OCD)

Sertraline is licensed for the treatment of OCD in children aged 6 years and above. Treatment should be initiated only by specialists. Fluvoxamine may be used to treat OCD in children aged 8 years and above.

No other SSRI/SNRI is licensed for anxiety disorders, including OCD in children in the UK. However, fluoxetine is licensed for OCD in children aged 7 years and above in the USA.

Previous CSM advice on SSRIs and suicidality

In 2000 we informed you of CSM's advice that suicidal thoughts and behaviour are likely to increase in the early stages of treatment of depression. Patient information leaflets for Selective Serotonin Reuptake Inhibitors (SSRIs) contain advice to seek medical attention urgently in the event of such symptoms.

CSM reviewed this issue most recently in December 2001 and concluded that the evidence was not sufficient to confirm a causal association between SSRIs and suicidal behaviour, although an effect in a small high-risk population could not be ruled out.

An Expert Working Group of the CSM has been convened to look at the wider issues relating to the safety of SSRIs, and will examine urgently what implications, if any, these new findings in the paediatric population have for the use of paroxetine in adults and for other SSRIs. The benefits of paroxetine in adults are well established in the treatment of depressive illness and anxiety disorders and are considered to outweigh the risks.

A tear-off factsheet is attached at the back of this edition which may be used to aid discussions with patients

Salmeterol (Serevent) and formoterol (Oxis) in asthma management

Prescribe only in conjunction with inhaled corticosteroids

The new British Thoracic Society/Scottish Intercollegiate Guidelines Network guidelines for the treatment of asthma recommend that long acting beta-2 agonists, such as salmeterol and formoterol should be used as "add-on" therapy in conjunction with inhaled corticosteroids[1].

The guidelines suggest that add-on therapies such as long-acting beta-2 agonists should be tried with inhaled corticosteroid doses as low as 200mcg/day, before increasing the inhaled corticosteroid dose (beclomethasone or budesonide) up to 800 mcg/day in adults and 400 mcg/day in children. Recent analysis of UK prescribing data on salmeterol and formoterol in primary care has shown that up to 30% of patients prescribed salmeterol or formoterol may not be taking concurrent inhaled corticosteroids[2].

For the maintenance treatment of asthma salmeterol and formoterol should be prescribed in conjunction with inhaled corticosteroids. Prescribers are also reminded that salmeterol and formoterol should not be used for the treatment of acute asthma symptoms, for which a short-acting bronchodilator should be given.

1. BTS/SIGN, Management of Asthma. A national clinical guideline. Thorax 2003; 54 (suppl 1): i1 – i94
2. As assessed by MHRA using IMS Disease Analyzer - MediPlus

Methotrexate and pneumonitis

New recommendations on monitoring for pulmonary symptoms

Methotrexate is a folate antagonist which is used to treat neoplastic disease, rheumatoid arthritis and psoriasis.

Up to 25 April 2003, a total of 90 UK reports of parenchymal lung disorders (including 52 reports of pneumonitis, 21 reports of pulmonary fibrosis, 5 reports of interstitial lung disease and 3 reports of interstitial pneumonits) have been received through the Yellow Card Scheme. In 17 of these reports the outcome was fatal.

Although pneumonitis is a well-recognised complication of methotrexate treatment, concerns have arisen about the increasing number of reports of this reaction received through the Yellow Card Scheme. This increase in reporting may reflect the increasing usage of methotrexate, particularly in the treatment of rheumatoid arthritis. Since many rheumatoid arthritis patients may have some degree of underlying lung disorder, they may have an increased susceptibility to developing pneumonitis.

The CSM has reviewed the available data and has advised that in order to minimise the risk of pneumonitis prescribers should:

- Inform patients of this risk and advise them to seek medical attention if they develop symptoms such as dyspnoea, dry non-productive cough or fever.
- Monitor patients for these symptoms at each follow-up visit.
- In the event of suspected methotrexate-induced pneumonitis, withdraw methotrexate and administer corticosteroids.

Please report any serious suspected adverse reactions to methotrexate via the Yellow Card Scheme.

Medicines containing peanut (arachis) oil

Peanut allergic patients should avoid these products

The CSM has reviewed allergic reactions associated with medicinal products containing peanut oil. Pharmaceutical grade peanut oil is refined and therefore the peanut protein should be removed during the manufacturing process. However, a study has demonstrated that very small amounts of peanut protein may remain in refined peanut oil[1].

CSM has advised that there is currently insufficient evidence to conclude that exposure to medicinal products containing peanut oil leads to **sensitisation** to peanut protein. However, although the risk of an allergic reaction is low, as a precaution CSM has advised that:

- Patients known to be allergic to peanuts should not use medicines containing peanut oil.
- As there is a possible relationship between peanut allergy and soya allergy, patients allergic to soya should also avoid medicinal products containing peanut oil.
- All medicines containing peanut oil are required to include an appropriate warning in the labelling.

1. Olszewski et al. Clinical and Experimental Allergy. 1998; 28: 850-859

Interaction between repaglinide (Novonorm▼) and gemfibrozil (Lopid)

Co-prescription is contraindicated

An interaction between repaglinide (Novonorm▼), a short-acting insulin secretagogue and gemfibrozil (Lopid), a lipid-lowering agent used to treat dyslipidaemia, has recently been reported[1]. When administered concomitantly, the blood glucose-lowering effect of repaglinide may be markedly enhanced and prolonged.

Worldwide, 5 spontaneous reports have been received of serious hypoglycaemic episodes in patients using repaglinide and gemfibrozil together. Three of these patients experienced hypoglycaemic coma, one of whom died. In some cases the patients were also taking other drugs and it is therefore not known whether the reactions can be solely attributed to an interaction with gemfibrozil. There have been no reports of interactions between repaglinide and gemfibrozil in the UK.

Any change in repaglinide pharmacokinetics caused by concomitant gemfibrozil administration is likely to be via inhibition of cytochrome P450 2C8. Other inhibitors of this enzyme, such as trimethoprim, may also enhance the effect of repaglinide.

Because of this interaction, co-administration of repaglinide and gemfibrozil is contraindicated. Based on the known metabolism of lipid-lowering agents, a similar interaction between repaglinide and other lipid-lowering agents is not expected.

1. Niemi M et al. Diabetologia, 2003; 46 (3): 347-351.

Sodium valproate and prescribing in pregnancy

The risk of congenital malformations in infants born to mothers receiving anti-epileptic medication is approximately 2 to 3 times higher than in the general population. An increased incidence of congenital malformations (including facial dysmorphia, hypospadias and multiple malformations, particularly of the limbs) has been demonstrated in infants born to mothers with epilepsy taking sodium valproate.

Two retrospective epidemiological studies have also suggested an association between in-utero exposure to sodium valproate and a risk of developmental delay[1,2]. Other factors, such as the mother's epilepsy, may also contribute to this risk.

Sodium valproate is the anti-epileptic of choice in patients with certain types of epilepsy such as generalised epilepsy with or without myoclonus or photosensitivity.

Following a review of the available data, including data from the UK Pregnancy and Epilepsy Register[3], CSM has advised the following:

- Women of childbearing potential should not be started on sodium valproate without specialist neurological advice.
- Women taking sodium valproate who are likely to become pregnant should receive specialist advice because of the potential teratogenic risk to the fetus.
- If taken during pregnancy sodium valproate should be prescribed as monotherapy at the lowest effective dose, in divided doses and if possible, as a prolonged release preparation.
- Folate supplementation prior to pregnancy may reduce the incidence of neural tube defects in infants born to women at high risk. Women should take 5mg folic acid **as soon as contraception is discontinued**.

1. Adab N et al. J Neurol Neurosurg Psych 2001; Jan (1): 15-21
2. Dean JCS et al. J Med Genet 2002; 39: 251-259
3. Craig et al. Epilepsia 2002; 43: Suppl 8, 079

Reactions in humans to veterinary medicines

Please report any incidents to the Yellow Card scheme or the VMD

Since 1985, the Suspected Adverse Reaction Surveillance Scheme at the Veterinary Medicines Directorate (VMD) has received approximately 300 reports of symptomatic reactions resulting from the accidental injection of veterinary medicines into humans. In addition, a recent survey has shown that the National Poisons Information Service receives approximately 100 such reports a year.

The data show that the majority (87%) of the reactions reported to the VMD are non-serious, with transient, mild, reversible symptoms such as pain and swelling. Less commonly moderate symptoms may result from secondary infection and may require medical attention. These are often associated with the use of multiple

dosing guns or with contaminated needles.

The severity of these reactions may be due to the site of the reaction, such as in a joint, but also due to the type of active ingredient or excipient. Accidental injection of a vaccine containing mineral oil into a finger can lead to ischaemia, necrosis and possible loss of the finger unless prompt medical attention is given, which may involve surgical incision and irrigation.

Reactions resulting from accidental injections of potent neurological agents such as etorphine hydrochloride and acepromazine maleate (Immobilon) can cause severe dizziness, cyanosis and respiratory problems due to the opioid action, and have resulted in deaths where the effect has not been reversed. The opioid antagonist naloxone should be given immediately.

Injection of the antibiotic tilmicosin (Micotil) may affect the cardiovascular system and can cause severe tachycardia. Please report any incidents via the Yellow Card Scheme or direct to the VMD (contact Mrs Burge on 01932 338427).

Sibutramine (Reductil▼): hypertension and tachycardia

Sibutramine (Reductil▼) is an anti-obesity drug which was licensed in Europe in May 2001 for the treatment of obese patients as part of a weight management programme. It is suitable for patients with a body mass index (BMI) of $\geq$30 kg/m^2, or those with a BMI of $\geq$27 kg/m^2 if other obesity related risk factors such as Type II diabetes or dyslipidaemia are present.

To date in the UK, approximately 130,000 patients have been prescribed sibutramine. Thriough the Yellow Card scheme the most commonly reported suspected adverse drug reactions (ADRs) include headache, hypertension, tachycardia, palpitations, chest pain, dizziness, insomnia, depression, anxiety, nausea and minor gastrointestinal symptoms.

Prescribers are reminded that patients administered sibutramine should have their blood pressure and heart rate monitored regularly. In the first 3 months of treatment, monitoring should take place every 2 weeks; between months 4 and 6 patient monitoring should take place every month and regularly thereafter, at maximum intervals of three months.

Treatment should be discontinued in patients who have a persistent increase in resting heart rate of $\geq$10 bpm or systolic/diastolic blood pressure of $\geq$10 mmHg. Patients should also be advised to consult a doctor urgently if symptoms such as progressive dyspnoea, chest pain and ankle oedema occur. Full guidance on prescribing is contained within the Summary of Product Characteristics.

Please report all suspected ADRs associated with sibutramine via the Yellow Card Scheme.

Pergolide (Celance) and cardiac valvulopathy

Pergolide (Celance) is an ergot derived dopamine agonist used primarily in the treatment of Parkinson's disease. It is indicated both as monotherapy and as adjunct therapy with levodopa. Since pergolide was first launched a small number of cases of cardiac valvulopathy have been reported. Of the estimated 500,000 people who have been treated with pergolide since 1989, valvulopathy has been reported in fewer than 5 in 100,000.

A case series has recently been published by the Mayo clinic[1]. Valvulopathy was limited to a single valve in some cases but involved multiple valves in others. The data from spontaneous reports and the published literature is suggestive of a potential association between pergolide and cardiac valvulopathy. However, definite conclusions regarding causality cannot be made at present.

Retroperitoneal, pleural and pericardial fibrosis are rare but well-known adverse effects of ergotamines. Even more rarely fibrosis of cardiac valves has been reported with ergot derivatives[2]. Whether the mechanism of the fibrotic valvular changes seen with ergot derivatives is related to retroperitoneal, pleural and pericardial fibrosis is not known.

Valvular changes related to ergotamines are anatomically similar, but not identical to those reported in carcinoid syndrome, except that in carcinoid syndrome the right-sided heart valves are primarily affected, while any valve may be affected by ergotamines.

The explanation most commonly postulated for ergot related valvular fibrosis is the overlap in receptor binding profiles between ergot derivatives and the monoamine serotonin.

1. Pritchett, MA et al. *Mayo Clin Proc.* 2002; 77: 1280-1286
2. Flaherty, KR & Bates, JR. *Am Heart Journal.* 1996; 191: 603-606.

Possible interaction between warfarin and cranberry juice

Patients taking warfarin should limit or avoid drinking cranberry juice

Cranberry juice (Vaccinium macrocarpon) is a popular drink that has also been used for the prevention of cystitis[1].

Since 1999, the CSM has received five reports suggesting an interaction between warfarin and cranberry juice, leading to changes in INR values.

One fatal case involved a man whose INR dramatically increased (INR>50) six weeks after starting to drink cranberry juice. This patient died from gastrointestinal and pericardial haemorrhage. In two cases, less dramatic INR increases were noted whilst patients were taking cranberry juice. In one of these the patient was stabilised on a lower dose of warfarin and in the other, the INR returned to the therapeutic range after stopping cranberry juice. In another case the INR was generally unstable, and in a further case an INR decrease was reported.

The interaction is biologically plausible since cranberry juice contains various antioxidants including flavonoids, which are known to inhibit cytochrome P450 activity[2], and warfarin is predominantly metabolised by the P450 isoform CYP2C9[3]. It is possible that the constituents of different brands of cranberry juice may vary, and that such variation might affect the potential for drug interactions. Whether constituents in cranberry juice can inhibit CYP2C9 and thus warfarin metabolism, or interact in another way will require further investigation.

Until this possible interaction between cranberry juice and warfarin has been investigated further it would be prudent for patients taking warfarin to be advised to limit or avoid drinking cranberry juice.

1. Kontiokari T et al. *BMJ* 2001; **322** (7302): 1571
2. Hodek P et al. *Chem Biol Interact* 2002; **139** (1): 1-21
3. Rettie AE et al. *Chem Res Toxicol* 1992; **5**: 54-9

Kava-kava and hepatotoxicity

Sale and supply of unlicensed Kava-kava prohibited

Worldwide, 75 cases of hepatic adverse reactions suspected to be associated with Kava-kava have been reported to date. These include cases of liver failure resulting in 8 liver transplants and 4 deaths. There have been 4 reports of liver toxicity in the UK suspected to be due to consumption of Kava-kava.

Kava-kava is considered to have the potential to cause idiosyncratic hepatotoxicity which may be serious. The exact frequency of these reactions is not known but is likely to be rare at normal doses. The mechanism of hepatotoxicity is not understood and there are no clear predictors.

On the basis of the data available, the CSM has recommended that the possible therapeutic benefits of medicinal products containing the herbal ingredient Kava-kava (*piper methysticum*) cannot be considered to outweigh the risks of hepatotoxicity[1]. Following a consultation on a proposal to prohibit the supply of unlicensed medicinal products for internal use containing Kava-kava, a prohibition order came into force on the 13 January 2003.

Healthcare professionals are reminded to ask about the use of Kava-kava and other herbal products in patients presenting with hepatotoxicity. Patients experiencing hepatotoxicity associated with Kava-kava have generally recovered on stopping Kava-kava. However, liver function should be monitored until recovery is complete.

Please report any past cases of hepatotoxicity associated with the use of Kava-kava and continue to report any suspected adverse reactions to herbal remedies via the Yellow Card scheme.

1. MCA/CSM Current Problems in Pharmacovigilance 2002; 28: 6.

Reminder: Gastrointestinal toxicity of NSAIDs

All NSAIDs, including ibuprofen and COX-2 inhibitors are associated with reports of serious gastrointestinal toxicity. The elderly and those taking concomitant aspirin are high-risk groups.

Detailed advice on the gastrointestinal safety of NSAIDs (including aspirin and selective COX-2 inhibitors) has previously been provided[1]. The CSM continues to receive reports of serious and fatal gastrointestinal reactions associated with NSAIDs.

Prescribers are reminded:

- GI risks of NSAIDs may be minimised by selecting the lowest dose for the shortest duration.

- Risks of GI toxicity are higher in the elderly.
- Aspirin and another NSAID should only be used together when absolutely necessary – the combination substantially increases GI risk. Patients taking long-term aspirin should be reminded to avoid NSAIDs, including those bought without prescription.
- Ibuprofen is associated with the lowest GI risk of the traditional NSAIDs, but serious and fatal GI reactions have been reported in association with its use.
- Clinical trial data suggest that selective COX-2 inhibitors have GI safety advantages over standard NSAIDs, but serious and fatal GI reactions have none the less been associated with these drugs.

Ensure NSAID treatment is not contraindicated before prescribing.

1. MHRA/CSM Current Problems in Pharmacovigilance. 2002; 28:5

Safety of thiomersal-containing vaccines

No evidence of neurodevelopmental adverse effects in children

Thiomersal is an ethylmercury-containing compound that has played an important role either as a preservative or in the initial stages of the manufacture of some vaccines for over 60 years.

The only childhood vaccines routinely used in the UK that currently contain thiomersal are the diphtheria, tetanus and wholecell pertussis (DTwP) vaccines and diphtheria and tetanus vaccines. Thiomersal is also present in some influenza and hepatitis B vaccines.

There is no thiomersal in MMR, single Hib, oral polio, meningitis C or BCG vaccines.

The mercury content of thiomersal has led to concerns that it may affect brain development in children when given in vaccines. The CSM has reviewed the available information relevant to this issue and has concluded that there is no evidence of neurological adverse effects caused by the very small amounts of thiomersal in some vaccines.

The World Health Organisation's Global Advisory Committee on Vaccine Safety (GACVS) has also kept this issue under review and concluded in November 2002 that there is no evidence of toxicity in infants, children or adults exposed to thiomersal in vaccines.

While there is no support for the belief that neurological adverse effects are caused by thiomersal in vaccines, the European Medicines Evaluation Agency recommended that it would be prudent to promote the use of vaccines without thiomersal as a precautionary measure. CSM has endorsed this recommendation and continues to do so. Manufacturers are therefore actively working to eliminate or reduce thiomersal in vaccines.

More detailed information about the safety of thiomersal containing vaccines can be found on the MHRA website (www.mhra.gov.uk).

CSM will continue to keep this issue under close review.

Dopaminergic drugs and sudden sleep onset

All dopaminergic drugs may cause somnolence

Possible sudden onset of sleep with pramipexole (Mirapexin) a treatment for Parkinson's disease, was highlighted in 1999[1]. A review of all dopaminergic drugs has recently been completed which reaches the following conclusions[2].

- Sleep disturbances can be a feature of Parkinson's disease.
- All dopamine agonists, to varying degrees have been associated with somnolence, which in some patients can be marked, particularly in patients with Parkinson's disease.
- A combination of the effects of dopamine agonists and the underlying disease may contribute to sleep disturbances in patients with Parkinson's Disease.
- Somnolence and episodes of sudden onset of sleep can impair driving ability.
- Drug combinations may worsen this adverse reaction.

Advice which takes account of the differing reporting frequencies has been added to products containing: levodopa (in combination with carbidopa/benserazide), dihydroergocryptine, piribedil, bromocriptine, pergolide, cabergoline, pramipexole, ropinirole, apomorphine, lisuride and quinagolide.

1. MCA/CSM Current Problems in Pharmacovigilance 1999; 25: 17.
2. European Agency for the Evaluation of Medicinal Products. CPMP Position Statement - Dopaminergic substances and sudden sleep onset - CPMP/578/02.

Yellow Card Scheme: your support is vital

In this edition of Current Problems in Pharmacovigilance you will find enclosed a Yellow Card for reporting of suspected adverse drug reactions (ADRs). The Yellow Card Scheme was introduced in 1964 after the thalidomide tragedy highlighted the urgent need for routine post-marketing surveillance of medicines. Since then more than 400,000 reports of suspected ADRs have been submitted to the Committee on Safety of Medicines (CSM) and the Medicines and Healthcare products Regulatory Agency (MHRA) on a voluntary basis by doctors, dentists, pharmacists and coroners and also by pharmaceutical companies under their legal obligations.

Why we need your support

The Yellow Card Scheme acts as an early warning system for the identification of previously unrecognised reactions. It also enables us to investigate in detail established ADRs in order to identify risk factors, outcome of the ADR and other factors that may affect clinical management. Better understanding of recognised reactions allows us to give advice on how medicines can be used more safely. The value of the Scheme has been demonstrated many times and it has helped to identify many safety issues. **The continued success of the Scheme is dependent on the vigilance of UK healthcare professionals and your willingness to report suspected ADRs. Every report can make a difference.**

What to report

Established medicines and vaccines

Please report all **SERIOUS** suspected adverse reactions to established medicines and vaccines.

Serious reactions include those that are:

- Fatal
- Life-threatening
- Disabling
- Incapacitating
- Congenital abnormality
- Involve hospitalisation
- And/or are medically significant

They should be reported even if the effect is well recognised.

New medicines and vaccines

Please report **ALL** adverse reactions (including those considered to be non-serious) suspected to be associated with black triangle (▼) medicines.

If you see the black triangle symbol ▼ this indicates that the CSM/MHRA are intensively monitoring that product.

Reactions in children

Please report **ALL** suspected adverse reactions that occur in children associated with *either* established *or* new medicines and vaccines.

What is the essential information to report

There are four critical pieces of information which must be included on the report. These include the name of the drug, the description of the suspect reaction, patient details such as the patient initials, age, sex, weight, or a local identifier and finally your (the reporters) details.

This enables us to acknowledge receipt of the report, and if necessary, request further information about serious reactions.

Where to find Yellow Cards

The electronic Yellow Card provides a quick and easy way to report and can be accessed by logging on to the following website: www.mca.gov.uk/yellowcard

A paper version of the Yellow Card is included in:

- British National Formulary (BNF)
- Nurse Prescribing Formulary (NPF)
- Monthly Index of Medical Specialities Companion (MIMS)

Where to get advice

For further information about the Yellow Card Scheme or to request Yellow Cards please contact us in one of the following ways:

✉ Write to us at: Medicines and Healthcare products Regulatory Agency, CSM FREEPOST, London, SW8 5BR

☎ Call the National Yellow Card Information Service on 0800 731 6789

Visit our website http://www.mhra.gov.uk **e**mail info@mhra.gsi.gov.uk

Current Problems in Pharmacovigilance is produced by the Committee on Safety of Medicines and the Medicines and Healthcare products Regulatory Agency.

Editorial Board: Professor G.Duff, Professor M. Kendall, Dr J.M. Raine, Dr P. Arlett, Miss S. Wark, Mrs L. Henderson

Enquiries, comments and suggestions to Mrs L. Henderson, Medicines and Healthcare products Regulatory Agency, Market Towers, 1 Nine Elms Lane, London SW8 5NQ

Dentists should notify a change of address by writing to Medical Mailing Company, Coltex House, Rectory Place, Loughborough, LE11 1TW, or by dialling the hotline number 0800 626387. Addresses supplied in connection with mailings on behalf of CSM and MHRA will not be used for other mailings without the permission of the individual concerned.

6. **How quickly will I feel a benefit?**

Many people feel benefit from treatment within 2-3 weeks. For some people, it may take longer. Even after you feel better it is important to keep taking your tablets for the period recommended by your doctor. For a small number of people an SSRI might not work at all.

7. **How long will my treatment last?**

Even when you feel better you should continue to take the medicine. If you suffer from depression this may be for 4-6 months or longer. You may need to continue taking the medicine for longer if you suffer from obsessive compulsive disorder or panic disorder.

8. **Will I have any trouble stopping taking these medicines?**

Some patients experience withdrawal/discontinuation symptoms when they stop taking these medicines. These can include feeling dizzy, shaky, sick, anxious, agitated or confused. Some people experience tingling sensations, pins and needles, burning sensations, electric-shock like sensations or find that they sweat more. Difficulty in sleeping and strange dreams can also occur.

If you are troubled by any of these withdrawal symptoms, your doctor may advise you to reduce the amount of medicine gradually by taking smaller amounts or taking the medicine less frequently for some time before stopping the tablets completely. Do not stop taking your medicine abruptly and do not stop taking your medicine without talking to your doctor first.

COMMITTEE ON SAFETY
OF MEDICINES

SSRI Factsheet

MHRA
Medicines and Healthcare products Regulatory Agency
Safeguarding public health

Key information for patients receiving treatment with medicines known as 'SSRIs'

1. What are the "SSRIs"?

The "SSRIs" or Selective Serotonin Reuptake Inhibitors are an important group of medicines used in the treatment of depressive illness and anxiety related disorders. There are a number of different medicines in the SSRI group and each has an individual name – Cipramil (citalopram), Faverin (fluvoxamine), Lustral (sertraline), Prozac (fluoxetine) and Seroxat (paroxetine). A similar medicine is Efexor (venlafaxine) which is known as a 'SNRI' or Serotonin Noradrenaline Reuptake Inhibitor. Efexor has the same indications and a similar safety profile as SSRIs and for this reason has been included in this factsheet.

2. How do SSRIs work?

Low levels of a substance called serotonin in the brain are thought to be a cause of depression and related disorders. SSRIs work by bringing the level of serotonin back up to normal.

3. Any special advice about starting on treatment?

SSRIs may not be suitable for everyone. It is important you talk to your doctor about any other medical conditions you may have (particularly epilepsy, diabetes, glaucoma, liver problems and kidney problems) or if you are or might be pregnant or breastfeeding. You should tell your doctor about any other medicines you may be taking, including those bought from a pharmacist or any herbal remedies.

4. What are the possible side-effects?

Any medicine can cause side effects in some people. For most people these side effects are not severe and they get better over time. The most common side effects of SSRIs are nausea (feeling sick), insomnia (difficulty sleeping), drowsiness, headache or a sense of feeling tense or nervous.

If you have trouble with any side effects, you should discuss them with your doctor or pharmacist. They may recommend that the amount of the medicine that you are taking should be reduced or that your medication should be changed. More detailed information on possible side effects can be found in the Patient Information Leaflet enclosed with your tablets.

5. Are SSRIs associated with a risk of suicide?

For a small number of people, there may be an increase in suicidal thoughts and behaviour in the early stages of treatment with any antidepressant, including SSRIs. This is nothing to be ashamed of. If you experience thoughts or feelings of suicide or wanting to harm yourself you should talk to your doctor as soon as possible.

NOT FOR PUBLICATION

COMMISSION ON HUMAN MEDICINES

PHARMACOVIGILANCE EXPERT ADVISORY GROUP

Minutes of the meeting held on Wednesday 2nd October 2013 at 10:30 in meeting room R-T-501-502, 5th Floor, 151 Buckingham Palace Road, SW1W 9SZ

MEMBERS PRESENT

Professor M Pirmohamed (Chair)
Dr R Bracchi
Dr W Dixon
Dr I Douglas
Miss A Ewing*
Professor D Gunnell
Professor S Maxwell
Dr K Miller +
Professor A Silman +
Professor P Waller
Mr P Willan
Dr C Vaughan

PROFESSIONAL STAFF OF MHRA

Principal Assessor

[redacted]

Supporting specific items

[redacted]

ITEM

[redacted]

MHRA Observers

[redacted]

Apologies

Dr J Coleman
Dr N Plant
Mrs A Sherratt
Dr R Thanacoody

Secretariat

[redacted]

* *participated via teleconference*
+ left the meeting at item 7

[redacted]

5.2.3 [redacted]

5.2.4 [redacted]

5.3 **Sodium valproate**
Use in pregnancy and risk of neurodevelopmental delay and autistic spectrum disorder: new data and need for a referral

5.3.1 Professor Pirmohamed declared a non-personal, non-specific interest in this item, which did not debar him from taking part in the discussion.

5.3.2 The EAG was presented with a summary assessment of the latest published study data on the risk of longer term potential neurodevelopmental effects, including autistic spectrum disorder, following foetal valproate exposure.

5.3.3 The EAG considered that the latest study data are robust and represent a substantial upgrade in evidence on the potential long-term neurodevelopmental effects.

5.3.4 The EAG agreed that the analysis of six-year follow-up data from the study by Bromley and Meador suggested a dose dependent effect for an association of lower IQ with foetal sodium valproate exposure that appeared independent of maternal IQ but no association was found for the other

antiepileptics included in this study. The EAG also agreed with the assessment that the studies by Christensen and Veiby provided evidence for an increased risk of neurodevelopmental delay whilst adequately controlling for maternal epilepsy.

5.3.5 The EAG noted that there are existing warnings in the sodium valproate product information but that this could now be considered to not fully reflect evidence from the most recently published studies which have provided further clarity on the magnitude and persistence of the risks.

5.3.6 The EAG noted that there is a lack of consistency in the product information available for the range of sodium valproate containing products across EU member states and therefore agreed that timely assessment and regulatory action at an EU level was considered necessary.

5.3.7 The EAG concluded that an Article 31 referral is warranted in order to fully evaluate the impact of the new data on the benefit/risk of sodium valproate in all of its authorised indications in the EU and what, if any, further regulatory action is required.

6 **Risk Management Plans**

New Application

6.1 [redacted]

6.1.1 [redacted]

6.1.2 [redacted]

6.1.3 [redacted]

NOT FOR PUBLICATION

COMMISSION ON HUMAN MEDICINES

Sodium Valproate Working Group

Minutes of the Meeting held on **Wednesday 26th February 2014** at **2.00pm** in **R-T-501/2, 5th Floor, 151 Buckingham Palace Road, Victoria, London SW1W 9SZ**

Members Present

Professor M Pirmohamed (Acting Chair)
Mrs A Bowser*
Mr S Dajani
Dr B Davies
Professor H Dolk*
Dr C Derry
Professor G Goodwin
Dr H McAllister-Williams
Dr K Miller
Carolyn, Lady Roberts
Dr P Santosh
Dr J Shakespeare
Mrs T Thomas
Professor P Waller
Dr J Winer*
Dr L Yates

*Via Teleconference

Professional Staff of MHRA

[redacted]

Observer

Dr R Bromley (University of Manchester

Apologies

Professor D Owens (Chair)
Dr M Jackson
Professor A MacGregor
Dr F O'Callaghan

Secretariat

[redacted]

1. Apologies and Announcements

1.1 The Chairman reminded all present that the papers and proceedings of the Working Group (WG) were confidential and should not be disclosed.

1.2 The Chairman reminded members that any personal specific, personal non-specific, non-personal specific and non-personal non-specific interests would have to be declared. Members were also asked to declare any other matter which could reasonably be perceived as affecting their impartiality. No interests were declared by members.

1.3 Apologies had been received from Professors Owens and MacGregor, and Drs Jackson and O'Callaghan

1.4 The Chair informed the WG that Mrs Bowser, Professor Dolk and Dr Winer would be participating via teleconference.

1.5 The Chair welcomed Dr Bromley as an Observer at the meeting. While Dr Bromley would take no formal part in the discussion, she would, at the Chair's invitation, comment on specific issues. Dr Bromley shared prepublication findings from the latest research conducted by the Liverpool group

2. Introductions

2.1 At the Chair's request, all participants introduced themselves.

3. Background and regulatory process

3.1 The Chair summarised the background to the need for the Group's advice in relation to the on-going European review examining the risk of neurodevelopment delay in children exposed to sodium valproate in utero, and emphasised the confidential nature of all items discussed.

4. Terms of Reference of the Working Group

4.1 The WG agreed the Terms of Reference as presented in Annex 1 to the minutes.

5. Paper for discussion - Risk of neurodevelopmental delay associated with sodium valproate in pregnancy

5.1 The WG considered the tabled comments from Professor Owens and MacGregor, and Dr Jackson.

5.2 MHRA presented slides to summarise the assessment of the data. Members' advice was sought on the following points:

5.2.1 To consider the evidence for an association between valproate exposure in

pregnancy and neurodevelopmental effects and autism spectrum disorder.

Definition of the Disorder

The WG considered noted that the latest published data [1,2] on outcomes of children exposed to sodium valproate in utero supported risk estimates for three separate conditions: Autism Spectrum Disorder (ASD), Childhood Autism and Intellectual disability as measured by IQ testing. The WG commented that a reduced verbal IQ would be expected in children with ASD due to difficulties in social communication which characterize this condition

In addition to the intellectual impairments identified in the studies, the WG added that affected children often had physical developmental delay but, with splinting and physiotherapy, many of the children with hypermobile joints do "catch up" with their peers. The WG advised that the data suggested that the IQ deficits following sodium valproate exposure in utero were permanent, without the possibility of any "catch up". This highlighted the suitability of the term "delay" to describe the neurodevelopmental problems cited in the current product information. The WG advised that impermanence was implied by the word "delay" and a more accurate term should be adopted to communicate the seemingly permanent nature of effects on intellectual functioning.

The WG advised that children affected often have features of ADHD, Autism spectrum disorder and intellectual disability.

Strength of Evidence

Applying the Bradford Hill criteria for causality, the WG concluded that the new epidemiological data provided very strong evidence for an effect of sodium valproate on neurodevelopmental function that was distinct to that of other antiepileptics studied. In the 15 studies specifically assessed there was consistency of effect, despite low numbers of patients in the smaller studies which did not allow sufficient statistical power to characterize effects.

The WG noted that there is a "cognitive function shift" to the left in the curve displaying the spread of IQ across all children exposed to sodium valproate in the Neurodevelopmental Effects of Antiepileptic Drugs- NEAD study, Meador et al 2013[1], and that this was not present for other antiepileptics studied. From the Meador,study IQ did improve in the sodium valproate-exposed group but did not reach expected levels, even after correction for maternal IQ.

[1] Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, Kalayjian LA, Kanner A, Liporace JD, Pennell PB, Privitera M, Loring DW; NEAD Study Group. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol. 2013 Mar;12(3):244-52

The WG advised that one third of children diagnosed with ASD suffered with epilepsy and, if poorly controlled, this could lead to memory problems – the WG advised that this may make some of the data on cognitive impairment difficult to interpret.

Data from the study by Christensen[2] were considered to be robust for the association between ASD and childhood autism in children exposed to sodium valproate.

It was acknowledged that there is a lack of data on the risk of neurodevelopmental problems in the children of women treated for bipolar disorder and that it is not known whether the risk is similar or very different.

Verbal presentation- pre publication Cochrane review data

The WG was provided with a verbal presentation of the findings from the Cochrane review which were to be published in the near future. The meta analysis performed for the review was noted to include prospective studies only. The main outcome was Global Cognitive Delay in children exposed to sodium valproate, carbamazepine and several other antiepileptic drugs, compared to a control group without epilepsy. The analysis identified a significant difference in global cognitive delay in the sodium valproate exposed group only, when compared to patients without epilepsy

The WG noted that the Cochrane review had not compared the risks associated with polytherapy and high dose monotherapy but there was a suggestion that high dose monotherapy may be associated with a greater risk of neurodevelopmental delay than polytherapy.

Biological Mechanism

The WG advised that a single mechanism for "cognitive teratogenesis" could not be established from the data presented. The WG emphasised the complexities of brain development and noted that the developing brain is vulnerable to drug-related injury at all stages of pregnancy and following parturition. In particular, neuronal migration disorders can occur beyond 20 weeks' gestation.

The WG noted that folic acid deficiency in pregnancy was linked to neural tube disorders. Since sodium valproate affected folic acid metabolism the value of folic acid co-administration in minimizing the risks to brain development should be assessed in humans. The WG advised that there was some evidence that women with genetic generalised epilepsy taking sodium valproate may not experience the same degree of risk reduction from folic acid, even for neural tube defects, and this requires further study.

[2] Christensen J et al. Prenatal valproate exposure and risk of autism spectrum disorder and childhood autism. JAMA.2013;309: 1696-1703

5.2.2 To consider the balance of risks and benefits of valproate in pregnancy, in women planning pregnancy and in women of childbearing potential in women with epilepsy and bipolar disorder.

Overall the WG suggested that the benefit:risk of sodium valproate could be positive in women of childbearing potential when restricted to severe generalised epilepsy and acute manic episodes in bipolar disorders in patients who have not responded to other treatments. The WG advised that several risk minimisation measures could optimise its safe use. In addition, several questions were proposed for the MAHs that would help better inform decisions on any possible risk minimisation measures.

5.2.3 To consider the place in clinical practice of valproate in its licensed indications.

Use of sodium valproate in treatment of epilepsy

The WG advised that in the UK sodium valproate is considered an important medicine in the treatment of genetic generalised epilepsy. For this form of epilepsy sodium valproate is considered first line treatment in males but not in females because of its effects on the fetus. The WG advised that there was a small proportion of the patient population with genetic generalised epilepsy which would respond only to sodium valproate. In focal epilepsies it is considered very rare that only sodium valproate provides adequate seizure control and several other therapeutic options are available.

The WG advised that, for female patients of reproductive potential with genetic generalised epilepsy sodium valproate would not be considered first line. Levetiracetam or lamotrigine are generally considered as first line treatment choices for female patients with generalised epilepsy

Use of sodium valproate in treatment of bipolar disorder

In psychiatric illness the WG advised that there is significant use of sodium valproate in not only the acute manic episodes but also “off label” for maintenance of mood disorders in bipolar and unipolar depression. Other “off label” use includes use in schizoaffective disorder and management of Borderline personality disorder. Unlike epilepsy the WG advised that there was no clear dose response in psychiatric indications. The WG advised that the decision to use sodium valproate in psychiatric indication was often driven by patient choice because of patient concerns about monitoring requirements and associated with lithium and concerns about risks in pregnancy. The WG advised that alternatives do exist for the management of bipolar disorder, most commonly antipsychotic drugs, which are recommended in NICE guidance on the management of this condition

Use of sodium valproate in unlicensed indications

The WG advised that, for migraine prophylaxis (which is not a licensed indication in the UK), sodium valproate is generally avoided in "fertile" female patients and is reserved as 3rd or 4th line treatment in male patients (endorsed with level 1 evidence by American Association of Neurologists). The WG expressed concern that private clinics often prescribe sodium valproate more freely for migraine prevention and this often occurs without counselling on the need for effective contraception. Sodium valproate is also used off label to manage cluster headaches.

5.2.4 To advise on appropriate measures to minimise risk associated with the use of valproate in pregnancy, taking into account use in unlicensed indications.

For the management of epilepsy the WG considered that there is a unique place for sodium valproate in some patients with genetic generalised epilepsy. However there are patients taking sodium valproate who do not necessarily need the medication and could take alternatives. The WG recommended that stronger warnings are included in the product information for other types of epilepsy. A restriction to use of sodium valproate in females with severe genetic generalised epilepsy was proposed by the WG.

The WG proposed that whatever communication is issued that it should be consistent across all of the indications for use of sodium valproate and try to take into account off label usage.

5.3 SVWG conclusions

5.3.1 The WG concluded that sodium valproate has an important place in the treatment of some types of epilepsy and in the treatment of acute mania in bipolar disorder.

5.3.2 Given the data the WG advised that the benefit:risk in generalised epilepsy was positive but that it should not be used first line in female patients/women of childbearing potential, rather, its use should be reserved for when other treatments have failed. The benefit:risk of valproate in focal epilepsy was less certain.

5.3.3 The WG advised that use in bipolar disorder should be restricted to the use in acute manic episodes when other treatments have failed. For use in migraine (not an approved indication in the UK) the balance of benefits and risks in women of child- bearing potential is considered to be negative

5.3.4 The WG advised that further information should be sought in a number of areasin particular 1) the relationship between valproate exposure and behavioural problems in children, 2) the relative risk of polytherapy vs. monotherapy, 3) the role of folic acid in risk minimisation, 4) use of valproate when breast feeding and any additional risk conferred by this, 5) the benefit:risk in focal epilepsy and 6) the effectiveness of current risk minimisation measures, particularly in acute manic episodes in bipolar disorder.

5.3.5 The WG advised that further work on appropriate risk minimisation measures to prevent unintentional pregnancy exposures to sodium valproate should involve a number of stakeholders, including patient groups or representatives in epilepsy and psychiatry.

6. Agreement of next steps

6.1 The proposal for further questions to the MAHs was endorsed and it was agreed that these would be finalised after discussion at the Pharmacovigilance Risk Assessment Committee meeting in April.

7. Any other business

None.

8. Date of next meeting - tbd

Annex I: Terms of Reference of SVWG

To consider the evidence for an association between valproate exposure in pregnancy and neurodevelopmental effects and autism spectrum disorder.

To consider the balance of risks and benefits of valproate in pregnancy, in women planning pregnancy and in women of childbearing potential in women with epilepsy and bipolar disorder.

To consider the place in clinical practice of valproate in its licensed indications.

To advise on appropriate measures to minimise risk associated with the use of valproate in pregnancy, taking into account use in unlicensed indications.

To advise the Commission on Human Medicines.

NOT FOR PUBLICATION

COMMISSION ON HUMAN MEDICINES

SODIUM VALPROATE WORKING GROUP

Minutes of the meeting held on **18th June 2014**, at **2pm** in **R-T-501/2 5th Floor, 151 Buckingham Palace Road, SW1W 9SZ, London.**

Members Present

Professor M Pirmohamed (Chair)
Mrs A Bowser
Professor D Coghill*
Ms N Crosby-McKenna
Dr K Darton
Professor H Dolk*
Mr M Harnor
Carolyn, Lady Roberts
Dr J Shakespeare
Professor E Taylor
Professor P Waller
Dr J Winer*
Dr L Yates

*Via Teleconference

Professional Staff of MHRA

[redacted]

Apologies

Mr S Dajani
Dr C Derry
Professor J Duncan
Professor G Goodwin
Dr M Jackson
Dr H McAllister-Williams
Dr F O'Callaghan
Professor David Owens
Dr T Thomas

Secretariat

[redacted]

1. Introductions, apologies and announcements

1.1 The Chair welcomed all attending Members including those joining via teleconference.

1.2 The Chair reminded Members that the papers and proceedings were confidential and should not be disclosed.

1.3 Members' interests were reviewed and no potential conflicts were identified.

1.4 The Group was notified of Members who had sent apologies. Written comments were received from Professor Guy Goodwin (Tabled Paper I).

1.5 The minutes of the first Working Group meeting on 26th February 2014 were reviewed and verified as a true record of the discussion.

2. Meeting format

2.1 Prior to the meeting Members had been provided with draft minutes from the 1st Working Group meeting (26th February 2014) for review, and a paper for review. The paper comprised the MHRA's assessment of Marketing Authorisation Holders' responses to a List of Questions arising from the article 31 referral examining the safety of sodium valproate when used in women of childbearing potential.

2.2 The agenda for the meeting involved: i) reviewing the project to date – background and regulatory process, ii) reviewing and approving the minutes from the 1st Working Group meeting and iii) questions arising from the assessment of the response to the List of Questions.

2.3 During the meeting a slide presentation was displayed summarizing the MHRA assessment and highlighting specific issues for discussion by the Working Group.

3. Review of project to date

3.1 The Group was presented with a summary reminding Members of the details of the project to date.

4. Review of 1st Working Group meeting minutes

4.1 The Group confirmed that the minutes were a true record of the discussion.

4.2 The Group noted comments from some members about the need to ensure a strong and effective regulatory response given the number of women exposed to valproate and the availability of less harmful treatments.

5. Questions arising from response to List of Questions

5.1 *Behaviour Assessment System for Children (BASC) and usefulness in predicting ADHD*

5.1.1 Ms Crosby-McKenna declared non-personal non-specific interests in several of the MAHs. This did not debar her from taking part in the discussion.

5.1.2 The Group considered the BASC score and its usefulness in predicting a future diagnosis of Attention Deficit Hyperactivity Disorder (ADHD).

5.1.3 The Group stated that the BASC score indicated some degree of ADHD risk in children but was not diagnostic; there were insufficient data available to describe how results for BASC may translate into a risk of ADHD.

5.1.4 Members noted that ADHD may be a non-specific behaviour problem or a feature of a wider disorder. While ADHD differs from autism and intellectual impairment it has features of both of these conditions.

5.1.5 Members considered that it was plausible for sodium valproate to increase the potential for ADHD to occur, given its generalized neurodevelopmental effects.

5.1.6 The Group concluded that the strength of the evidence supporting a causal relationship between sodium valproate exposure and ADHD was weak; in available studies some cases were diagnosed before the age of one, which would not happen in clinical practice.

5.1.7 To further evaluate any association between sodium valproate and ADHD the Group recommended that i) the feasibility of using large Scandinavian observational databases could be investigated, ii) the Clinical Practice Research Datalink could be investigated, and iii) publications by Skoglund and Larson on Swedish databases could be reviewed.

5.2 *Effects of in utero exposure to sodium valproate on motor development*

5.2.1 The Group noted that most of the cases of motor impairment reported in the innovator company's safety database were assessed at one year of age. Generally the phenotypes of these patients were poorly defined.

5.2.2 The Group considered it to be very important to determine if motor impairment can occur following exposure to sodium valproate in utero as a distinct entity separate to the better-known neurocognitive effects or congenital abnormalities.

5.2.3 The Group recommended that existing prospective cohorts in the UK and EU should be reviewed and the children's phenotypes described with respect to motor impairment. A retrospective review of casenotes could be undertaken

and children with motor impairment at one year of age followed up to determine if the effects persisted. A study by Dean[i] et al involved a group of geneticists who characterized the phenotypes of children exposed to antiepileptics who developed motor and speech impairment – the approach taken in this study was considered a helpful guide to how similar work might be performed in existing cohorts.

5.3 ***Dose-dependent adverse effects of sodium valproate***

5.3.1 The Group stated that there may be an interaction between a genetic predisposition to teratogenic effects in the mother, and exposure to sodium valproate, leading to adverse effects in offspring. While the risk may increase with increasing dose, adverse effects in offspring also occurred at the low end of the dose range.

5.3.2 The Group considered that the lowest effective dose of sodium valproate should be used by women of childbearing potential, in the absence of any alternative treatment.

5.3.3 The Group acknowledged the existing wording in the sodium valproate SPC stating that valproate should be administered in divided doses, and noted that there is no evidence of harm associated with this approach.

5.4 ***Effects of folic acid supplementation on teratogenicity of sodium valproate***

5.4.1 Members noted that the recommended dose of folic acid was 5mg daily in women considered to be at high risk of teratogenic effects due to sodium valproate, and that treatment with folate should commence prior to conception.

5.4.2 The Group commented that there was little evidence for a greater beneficial effect of 5mg of folate daily in women receiving valproate, compared with the standard dose in pregnancy of 400mcg daily, but was content that 5mg should continue to be recommended in those at high risk.

5.5 ***Use of sodium valproate during breastfeeding***

5.5.1 The Group noted that there was currently no evidence of an adverse effect on infants from maternal use of sodium valproate while breastfeeding. The Group referred to a recent study which showed no evidence of neurocognitive impairment at 6 years in children whose mothers had received valproate while breastfeeding.

5.5.2 The Group recommended that pregnant women receiving sodium valproate should be counselled about the benefits of breastfeeding in light of the data (albeit limited) which showed that there was little risk to offspring from exposure via breastmilk.. The Group recommended that advice on lactation

should be included in any communications resulting from the article 31 referral.

5.6 ***Benefit-risk of sodium valproate in different indications***

Epilepsy

5.6.1 The Group agreed that sodium valproate should not be used in women of childbearing potential for the treatment of focal epilepsy unless there was no effective alternative.

5.6.2 Use of sodium valproate in generalised epilepsy was considered acceptable in situations where other treatments are considered to be ineffective or not tolerated

5.6.3 The Group made reference to relevant sections of current NICE guidance on managing epilepsy in adults to inform discussions

Bipolar disorder

5.6.4 The Group noted that the risk of developmental problems in the offspring of mothers with epilepsy and bipolar disorder may be different since there may be a greater genetic predisposition to teratogenicity in women with epilepsy.

5.6.5 The Group commented that recent evidence suggested there was no benefit of sodium valproate in the treatment of mania in patients aged up to 18 years of age.

5.6.6 The Group acknowledged the efficacy of valproate in adults with bipolar disorder and noted that it may have particular advantages in the treatment of rapid-cycling bipolar disorder. In adults, valproate may be preferred to lithium as a treatment for bipolar disease because it did not require plasma monitoring and it may act quicker than lithium in acute mania.

5.6.7 The Group agreed that sodium valproate may be necessary as a treatment for bipolar disorder in some women of child-bearing potential, but that it should be used rarely, even in acute mania, in that population.

Migraine

5.6.8 The Marketing Authorisation Holders for sodium valproate submitted no information to support the benefit-risk of sodium valproate in the treatment of migraine. The Group recommended that valproate should not be used in that indication.

5.6.9 ***Risk minimisation measures for use of sodium valproate in women of child-bearing potential***

Women of child-bearing potential who are not pregnant

5.7.1 The Group considered that sodium valproate should only be used in women of child-bearing potential in situations where other treatments are considered to be ineffective or not tolerated

5.7.2 The Group stated that existing patients should have the benefit-risk of continued valproate treatment reviewed in secondary care, noting that some women may receive infrequent reviews if stable on long-term treatment. Valproate treatment should not be commenced in primary care for any indication.

5.7.3 In considering communications to healthcare professionals and patients, the Group stated that patients established on long-term treatment with valproate should be addressed as well as potential new users.

5.7.4 The Group recommended that the cognitive teratogenic potential of valproate should be emphasized to neurologists and psychiatrists as the risk of developmental disorders may be less well-known . Perinatal psychiatrists were also considered important to include.

Women of child-bearing potential who are pregnant

5.7.5 The Group noted that the risk of neurocognitive impairment from valproate exposure probably existed throughout pregnancy.

5.7.6 The Group recommended that in women with epilepsy receiving valproate who experience an unplanned pregnancy, the risk of changing to a different antiepileptic drug should be weighed against the risk of continuing valproate treatment. Little data were available on this and current guidelines tended to discourage changing antiepileptic drugs during pregnancy.

5.7.7 The Group recommended that the pregnancy registry in Belfast supervised by Dr James Morrow should be reviewed for any data on changing antiepileptic drugs during pregnancy.

5.7.8 The Group noted that some women may not comply with their usual antiepileptic treatment while pregnant.

5.7.9 Similarly the Group noted that discontinuing treatment for bipolar disorder during pregnancy could be life-threatening. This was usually done gradually over several weeks and an antipsychotic medication commenced. Further advice from an adult psychiatrist was recommended.

Infants exposed to sodium valproate in utero

5.7.10 The Group recommended that children exposed in utero to valproate should be referred early for a neurological assessment.

5.8 ***Proposed regulatory actions***

5.8.1 The Group agreed that the appropriate restrictions for use of sodium valproate in all indications were:

1) In female patients, restriction of sodium valproate to use where other treatments are ineffective or are not tolerated.
2) Provision of appropriate counselling to women and signed acknowledgement of risks, annually, including that:
    i. The patient understands the expected risk to the unborn child.
    ii. The patient understands the need for effective contraception, without interruption, 4 weeks before starting treatment, throughout the entire duration of treatment, and 4 weeks after the end of treatment.
    iii. The patient is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy.
    iv. The patient acknowledges that she understands the hazards and necessary precautions associated with the use of sodium valproate.

5.8.2 The Group acknowledged the challenges of securing informed consent for valproate treatment from women with acute mania, as many of these are treated under section in hospital. Reference was made to the Mental Capacity Act 2005 as a source of information on the provision of acknowledgement or consent to treatment.

5.8.3 The Group recommended that the MHRA should partner with patient groups and Marketing Authorisation Holders on the wording of patient booklets and communications. The Group recommended that the Royal College of Psychiatrists and the Association of British Neurologists should be used to communicate to healthcare professionals.

6. Summary of action points

6.1 For ease of review the next steps agreed at the meeting are summarized below.

1) Investigate observational databases which could be used to study an association between valproate exposure in utero and ADHD in later life (Scandinavian databases [Sweden, Denmark, Norway], CPRD, database used by Christiansen et al).
2) Review publications by Skoglund and Larson on the use of Swedish observational databases for information on how to conduct a study of ADHD in those exposed to valproate in utero.
3) Examine existing prospective cohorts in the UK and EU which have gathered data on outcomes following valproate exposure in utero, and characterize the phenotypes of the children with respect to motor impairment.
4) Review the study by Dean et al which gives a good example of how paediatric phenotypes have been characterized in other work.

5) Review the pregnancy registry data collected in Belfast for information on switching antiepileptic medication duration pregnancy.
6) Request advice from an adult psychiatrist to understand the usefulness of valproate in the treatment of bipolar disorder in adults and to understand the possible consequences of restricting use in this group.
7) MHRA to collaborate with patient groups and Marketing Authorisation Holders on the wording of patient education and communication materials about the use of valproate in women of childbearing potential.
8) MHRA to use the Royal College of Psychiatrists and the Association of British Neurologists as a means of communicating to healthcare professionals the updated advice on use of valproate in women of childbearing potential.

7. Meeting summary and conclusions

7.1 While considered to be biologically plausible, there was currently insufficient information available to confirm an association between valproate exposure in utero and the development of ADHD in children.

7.2 Further work should be undertaken to identify whether motor impairment can occur in children exposed to valproate in utero independent of congenital abnormalities or neurocognitive impairment. There was currently insufficient information available to confirm a risk of isolated motor impairment.

7.3 Since there was probably a risk of neurocognitive impairment in the offspring of women taking valproate at even the lowest approved dose, it was important that the lowest effective dose was used by women of childbearing potential, in the absence of any alternative treatment.

7.4 The current recommendation for use of folic acid supplementation 5mg daily in women of childbearing potential receiving valproate was endorsed.

7.5 The risk to the infant from exposure to valproate in breastmilk was not known, but limited data are reassuring. Women should be counselled accordingly.

7.6 Sodium valproate should not be used by women of childbearing potential for the treatment of migraine.

7.7 Across all approved indications, women of childbearing potential should be treated with valproate only if other treatments are ineffective or are not tolerated, under specialist supervision and subject to regular review of the need for treatment.

7.8 Women who received valproate should be given appropriate counselling and sign an ‘acknowledgement of risks’ form every year.

7.9 Women of childbearing potential who were established on valproate treatment should have a benefit-risk assessment performed in secondary care. Valproate should not be commenced for any reason in primary care.

7.10 The benefits and risks of switching treatment should be assessed in women who become pregnant while receiving valproate.

7.11 Children exposed to valproate in utero should be referred early for a neurological assessment.

7.12 Education and communication about the risks to the foetus of valproate exposure in utero should be provided to both patients and healthcare professionals on the conclusion of the article 31 referral. The wording of these materials should be agreed by regulators, Marketing Authorisation Holders and patient groups. Professional bodies should be used as a means to communicate to healthcare professionals.

8. Date and time of next meeting

8.1 It was agreed that Members will be notified at a future date if a third meeting was required.

Membership of the CHM Working Group on Sodium Valproate

Attending Members

Professor Munir Pirmohamed[ii] MB ChB (Hons) PhD FRCP FRCP(E) FMedSci
David Weatherall Chair of Medicine, NHS Chair of Pharmacogentics & Director of the Wolfson Centre for Personalised Medicine **(CHAIR)**

Mrs Alison Bowser[iii]
Patient and Public Involvement Officer, Research Design Service, Southampton University

Professor David Coghill MD ChB MD
Reader in Child and Adolescent Psychiatry, University of Dundee

Ms Nicole Crosby-McKenna
Senior Policy and Campaigns Officer, Epilepsy Action

Dr Katherine Darton BA BSc PhD LGSM
Lay member

Professor Helen Dolk DrPH (Via Teleconference)
Professor of Epidemiology & Health Services Research, University of Ulster

Professor Guy Goodwin FMedSci
WA Handley Professor of Psychiatry University of Oxford

Mr Michael J Harnor[iii] MSc MEd
National Chairman of British Epilepsy Association (Epilepsy Action), Chair of The Greater Manchester Neurological Alliance

Dr Finbar O'Callaghan MA MB ChB MSc PhD FRCPCH FRCP
Reader in Paediatric Neuroscience, University College London. Consultant Paediatric Neurologist, Great Ormond Street Hospital for Children

Carolyn, Lady Roberts[iv] RGN RHV MSc
Member of The Ethox Foundation-Oxford Centre for Ethics and Communication in Healthcare
Practice. Health visitor

Dr Judy Shakespeare, GP RCGP
Clinical Champion in perinatal mental health, representing the RCGP

Professor Eric Taylor FRCP FRCPsych FMedSci
Professor of Child and Adolescent Psychiatry, King's College, London

Professor Patrick Waller[v] BMedSci MD MPH FRCP Ed. FFPM FBPharmacolS
Honorary Professor, Faculty of Epidemiology and Public Health, London School of Hygiene and Tropical Medicine

Dr John B Winer[iii] MB BS MRCP MSc (Immuno) MD FRCP (Via Teleconference)
Consultant Neurologist, Queen Elizabeth Hospital, Birmingham

Dr Laura Yates MBChB DRCOG MRCPCH PhD
Consultant in Clinical Genetics, Institute of Genetic Medicine, International Centre for Life, Newcastle–upon-Tyne

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[i] Dean JC, Hailey H, Moore SJ, Lloyd DJ, Turnpenny PD, Little J. Long term health and neurodevelopment in children exposed to antiepileptic drugs before birth. J Med Genet. 2002 Apr;39(4):251-9.
[ii] Chair PEAG, Member CHM
[iii] Member CHM, Member GRIDEAG
[iii] Member NPPEAG
[iv] Member CHM, Member MWHEAG
[v] Member PEAG

NOT FOR PUBLICATION

COMMISSION ON HUMAN MEDICINES

Minutes of the meeting held on Thursday 11th December 2014 at 10:00 in RT-501-503, 5th Floor, 151 Buckingham Palace Road, Victoria, SW1W 9SZ

Commissioners Present
Professor S H Ralston (Chair)
Professor D Ashby
Mrs A Bowser
Professor J Darbyshire
Dr J C Forfar
Dr J Fraser
Professor M Gore
Ms A Hoey
Professor M Macleod
Dr R Mann
Dr S Misbah
Professor B K Park
Professor M Pirmohamed
Professor S Price
Lady Roberts
Professor K M G Taylor
Dr A Thomas
Professor S H L Thomas
Professor I V D Weller (Vice Chair)

Apologies
Professor J Friedland
Professor D G C Owens

Invited Experts
Dr B Bannister
1 Professor C O'Callaghan

Secretariat
[redacted]

Observers
Department of Health
2 [redacted]

Ghanaian Food and Drugs Authority
3 [redacted]

Professional Staff of MHRA Present
Principal Assessors **Item**
[redacted]

Licensing
[redacted]

VRMM
[redacted]

13.2 National implementation of EU agreed risk minimisation measures for sodium valproate **Sanofi Aventis**

13.2.1 Professor Ralston and Ms Hoey declared non-personal non-specific interest in Merck, Sharp and Dohme (MSD) and Professor Ashby non-personal non-specific interest in MSD and Sanofi, but this did not debar them from taking part in the proceedings.

13.2.2 The Commission noted Tabled Papers VII, VII(a) and VIII.

13.2.3 The Commission considered a paper summarising the conclusions of the European Article 31 review on the safety of use of sodium valproate in pregnancy and was asked to advise on plans for the UK implementation of the risk minimisation measures which had been agreed as the outcome of the referral. The Commission noted that work was ongoing with the Department of Health (DH), NICE and the MHRA.

13.2.4 The Commission endorsed the need for better information to be made available to patients on the risks of developmental disorders in children exposed to sodium valproate in utero. The Commission discussed the proposal for an acknowledgement of risk form to be signed by the prescriber and patient. While the Commission noted that such a form was used as part of the pregnancy prevention plan for isotretinoin, it advised that the therapeutic context of valproate use was very different and raised complex issues around communication and understanding of risk. The Commission considered that patients should be provided with written as well as verbal information about the risks and benefits of the product but that the form proposed may not be the best tool to ensure the discussions between doctors and patients take place. The Commission advised that the MHRA should consult the existing General Medical Council (GMC) guidance on obtaining and recording consent and incentivise the necessary discussions via collaboration with the GMC.

13.2.5 The Commission advised that a multi-stranded approach to communication was needed and endorsed the collaboration between MHRA, NICE and DH. The Commission noted that the NICE epilepsy guidance included valproate as a first line treatment in some forms of epilepsy. The Commission advised that there should be consideration of communication tools with proven effectiveness such as Decision Aids, consideration of learning tools tailored to individual groups of patients including audiovisual aids and reminders for health professionals using electronic prescribing systems. The Commission endorsed the need for MHRA to send a letter to healthcare professionals and an article in Drug Safety Update on the agreed risk minimisation measures.

13.2.6 The Commission advised that communications on the regulatory outcome should be co-ordinated with communications from DH and NICE to ensure that consistent messages were delivered to healthcare professionals and patients at the same time.

NOT FOR PUBLICATION

COMMISSION ON HUMAN MEDICINES

SODIUM VALPROATE EXPERT WORKING GROUP

Minutes of the meeting held on Wednesday 2nd August 2017 at 3pm in R-T-501 & 502, 5th Floor, 151 Buckingham Palace Road, Victoria, London SW1W 9SZ

Members Present

Professor Sir M Pirmohamed (Chair)
Professor J H Cross*

Dr M Duerden
Professor J Lawrence
Dr Janine Lynch
Dr Rebecca Mann
Dr Karen Miller
Dr F Rugg-Gunn
Ms L Russell
Professor P Smith
Mrs M Wang

Apologies

Professor C Nelson-Piercy

Invited Experts

Professor T Barnes

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessor	Item
[redacted]	[redacted]

Supporting specific items

[redacted]

Others

[redacted]

* Participation from 15:12 PM from item 4

1 Introductions, apologies and announcements

1.1 The Chair welcomed all attending Members and Invited Experts. All Members and Invited Experts introduced themselves.

1.2 The Chair reminded Members, Invited Experts and Observers that the papers and proceedings were confidential and should not be disclosed.

1.3 The Chair reminded Members and Invited Experts present to declare their personal specific, personal non-specific, non-personal specific and non-personal non-specific interests in the agenda items if they had not done so prior to the meeting.

Members were asked to declare interests in the associated companies, listed below, and any close involvement with the product Sodium Valproate.

- **Aventis**
- **Destin**
- **GL Pharma**
- **Noridem**
- **Norton**
- **Ratiopharm**
- **Teva**
- **Winthrop**
- **Wockhardt**
- **Sanofi**

The Chair directed participants to Tabled Paper II – register of interests declared by Chair, Members and Invited Experts, which was circulated to the Chair, Members and Invited experts in advance of the meeting. All interests declared are listed at Annex A on page 9 to the minutes.

1.4 Members' interests were reviewed against the Conflict of Interests Policy for the Sodium Valproate Expert Working Group and no potential conflicts were identified.

1.5 The Group was notified of Members who had sent apologies. Apologies were received from Professor Nelson-Piercy. Written comments were received from Dr JP Leach (Tabled Paper I).

2 Background Papers

2.1 Prior to the meeting Members had been provided with four papers describing:

- The Terms of Reference of the group
- UK implementation of risk minimisation measures
- A summary of the EU Referral
- Consideration of the need for any interim national regulatory action pending the outcome of the Referral that aims to review the effectiveness of risk minimisation for sodium valproate when used in women of childbearing potential.

2.2 During the meeting a slide presentation was displayed summarizing the UK risk minimisation implementation and highlighting specific issues for discussion by the Working Group.

3 Terms of Reference of Sodium Valproate Expert Working Group

3.1 The Group was presented with the drafted Terms of Reference and these were endorsed by all members without further amendment:

- To review the current risk minimisation measures in place and possible reasons for lack of effectiveness
- To consider further regulatory measures required to minimise the risk of valproate use in pregnancy including (but not limited to):
    - a contraindication for use in pregnancy or in girls and women without effective contraception,
    - a formal Pregnancy Prevention Program
- To consider other measures required across the healthcare system to ensure compliance with the regulatory position in clinical practice (e.g. shared care agreements, registries)

and to advise the Commission on Human Medicines.

4 Implementation of Risk Minimisation Measures in UK

A presentation summarised the actions taken in the UK to implement risk minimisation measures agreed in the EU Referral which concluded in 2014, the latest CPRD data on monitoring effectiveness of risk minimisation, recent action by the brand leader to reissue existing materials and additional communications to highlight the role of the pharmacist and the latest EU Referral initiated in March 2017.

4.1 The Group asked about timelines and noted that the Referral was due to be complete in early 2018.

4.2 The Group noted that the message communicated so far of a 30-40% risk of developmental disorders related to those with a deficit measurable in the studies and some members, based on anecdotal experience felt that almost all babies, born to mothers who had taken valproate during pregnancy, could be affected to some degree.

5 Discussion of Drug Utilisation Data

The Group discussed the impact of risk minimisation in the different clinical settings, via an analysis of CPRD data .

5.1 Paediatric use of sodium valproate

The Group commented that the decrease in use of valproate in adolescent girls was encouraging and noted that the monitoring of valproate use in those girls aged 0-11 year was not a good marker of the effectiveness of risk minimisation.

5.2 Bipolar disorder

The Group noted that valproate was generally considered less effective than antipsychotics in the treatment of bipolar disorder and that this was reflected in clinical guidelines. The Group noted results from an audit comprising 55 mental health trusts in England showing that a third of patients treated for bipolar disorder are taking valproate and a quarter being prescribed Lithium. The preference for valproate over lithium might be related to the requirement for blood test monitoring with lithium and that lithium was not without a risk of significant side effects. In women of childbearing potential (aged under 50 years in this study), a quarter were prescribed valproate mainly for hypomania and relapse prevention. By comparison, 43% of male patients were prescribed valproate for mania and aggression. The Group noted the gender differences in usage may reflect some recognition of the teratogenic risk of valproate.

5.3 The Group noted an audit conducted in East London and Manchester that showed no evidence of reduced doses being used with most women (90%) on a dose of above 1g daily (average 1.196g). In the same audit, there had been no assessment of benefit and risk in over 25% of patients. One study showed that only 6/74 female patients had received the MHRA risk minimisation documents. Another study showed that approximately 50% of female patients included had received information about contraception and teratogenic risk, it was commented that this was double the number of women informed in the previous audit 10 years before by James et al.

5.4 The Group noted that the British Association of Psychopharmacology 2017 guideline effectively contraindicates the use of valproate in bipolar disorder in females of child bearing age and that it was much less common that a woman with bipolar disorder could only be controlled on valproate in comparison to women treated for epilepsy. The Group noted that in psychiatry, quetiapine and olanzapine were effective alternatives to valproate. Although valproate could be useful in an in-patient setting, some of these patients could return to care in the community without review of the suitability of their medication longer term.

5.5 The Group noted that in some patients with bipolar disorder, achieving long term stability may require combination therapy which could include valproate. The Group noted the difficulty of compliance with contraception in patients with bipolar disorder.

5.6 Epilepsy

The Group agreed that the need for valproate as a therapeutic option in the treatment of epilepsy was greater than that for bipolar disorder. The Group noted that an audit of the use of valproate in University College Hospital showed that only half of all valproate prescriptions issued by for neurologists or psychiatryists, while the other half of prescriptions were issued by other specialists including oncology and gastroenterology for neurology and psychiatry indications.

5.7 The Group noted that generally if a patient was under the care of a neurologist they were likely to have unstable epilepsy. In these patients, the risks associated with valproate were well managed. The Group considered that it was the cohort of patients in the community receiving repeat prescriptions for sodium valproate that required better

risk management.

5.8 The Group discussed the transition which patients with epilepsy make from paediatric to adult services, and noted that in paediatric care the initiation of valproate prescribing was always undertaken by a specialist with extensive training. There was a system of transition defined as preparation for transfer to adult services at the appropriate age. In some areas, this included joint paediatric/adult clinics but this was not the case everywhere. Many teenagers whose epilepsy was stable on treatment were transferred to general practice.

5.9 The Group noted that in general practice there were often patients entering a practice from other areas of the country or overseas who were already taking valproate for a variety of conditions, including migraine, and that patients were reluctant to have the discussions with their GP that might lead them to having to stop the medication particularly when initiated in private headache clinics. The Group noted case details of individual patients with epilepsy and learning disability, bipolar disorder and migraine whose condition remains stable on treatment with valproate. All the patients mentioned that they had been informed of the risks and took appropriate risk minimisation measures. The Group noted that patients with learning disabilities could have problems understanding the risk communications materials and emphasised it was a challenge to get patients to return for follow up visits for contraception and regular counselling and that women may only return for a consultation when already pregnant.

6. Current Risk Minimisation Measures

6.1 The Group discussed the current risk minimisation materials and noted that they were generally good; however the lack of uptake may be related to accessibility and availability of the materials. The Group noted examples of where the risk of valproate was being miscommunicated with online forums, charity websites and some NHS trusts putting out advice inconsistent with approved materials. The Group noted the importance of the record of discussion form to be completed at every consultation with the prescriber to emphasise the messages.

6.2 The joint NHSI/MHRA Patient Safety Alert which had been sent in April 2017 was discussed. MHRA agreed to follow up with NHSI and to report back to the next meeting of the group on how many organisations had confirmed that they had implemented the actions required. The Group noted the learning video aimed at GPs and agreed that the current initiatives to widen the audience to pharmacists would be important.

6.3 In relation to awareness of pharmacists, the group noted that the toolkit materials were being redistributed by the brand leader in July and August and the new shelf marker, posters and hard copy toolkits were addressed to pharmacies rather than pharmacists. The Group suggested that a communication directed to individual pharmacists would be better received and advised that the Medicines Management Teams should be targeted in each CCG so that the message reaches more pharmacists.

7. Proposals for Additional Risk Minimisation Measures

7.1 The Group discussed options for increasing Pharmacists' awareness and agreed that the risk minimisation measures could be communicated in a Centre for Pharmacy

Postgraduate Education (CPPE) module and that this could be taken forward by liaison with the Pharmaceutical Services Negotiating Committee. An update to the existing Royal Pharmaceutical Society Quick Reference Guide for pharmacists would be timely since there is scope to improve the current one in the light of experience. In addition, a valproate "red box" on dispensing software would be a useful tool.

7.2 The Group discussed the effectiveness of the current valproate alerts on GP prescribing software and noted that they could be overlooked by GPs, unlike the methotrexate warning in prescribing software that required certain tests to be entered into the system before the prescription could be issued. In addition, the current IT systems contained an alert for valproate on initiation only, and this is not effective in general practice when repeat prescriptions are issued. In addition, the Group noted that there had been discussions between MHRA and NHS Digital as well as software providers on this issue and advised that improved prescribing alerts for valproate be further explored.

7.3 The Group noted that valproate prescribing was not currently the subject of a Shared-Care agreement. The Group advised that even though traditional models of shared-care relied on recording some form of monitoring of blood test results or similar, a shared care agreement could be set up with the results of certain tests and activities recorded in a red box on IT systems that prevented progressing the prescribing process until all are checked. The Group advised that implementing a formal shared care agreement for valproate should be further explored.

7.4 Pregnancy Prevention Program

The Group discussed the implementation of a formal pregnancy prevention program (PPP) for women of childbearing potential on sodium valproate. The Group noted that there are in-patient prescribing systems which have a warning message and link to materials with a reminder to discuss the risks that could be easily implemented more widely but was short of a full pregnancy prevention programme.

7.5 The Group discussed that implementing a formal PPP would not only minimise the risk of foetal exposure to sodium valproate but highlight the seriousness of the risk to both health professionals and patients. The Group noted that the additional burden may be manageable given the small, and decreasing, number of patients this would apply to. The Group acknowledged that the burden of a PPP would largely fall to general practitioners but that the benefits of an appropriately targeted system to prevent unplanned pregnancies and minimise the risk of exposure in pregnancy could be administered within a Shared-Care Agreement. A PPP would have the added advantage of standardising practice and minimising misinformation that is currently available on the internet. The Group noted that a letter to GPs could be issued by neurologists (via the ABN) to facilitate review of existing patients on valproate in secondary care, and that neurologists would be happy to review promptly patients currently on long term treatment. The Group noted that since referral to the neurologist would incur burdens on general practice, this should be factored into any arrangement for such referrals.

7.6 The Group noted concerns about prescribing valproate in patients with epilepsy who refuse or are unable to comply with the PPP requirements for contraception, and concerns about compliance with a PPP in terms of getting the patients to keep appointments. The Group also discussed the need to be aware of additional burdens on

patients and to consider the special needs of adolescents.

7.7 The Group noted that the long-acting reversible methods of contraception were highly effective and to be encouraged, but that access to and funding of Family Planning services were apparently variable across the country.

7.8 The Group discussed that a PPP would be feasible in psychiatry practice particularly given the very small numbers of eligible patients who could only be controlled by valproate, the maintained contact with specialist care, and the less immediate risks from symptoms of uncontrolled disease that could be easily detected by patients and carers.

7.9 The Group explored the retinoid PPP and the differences between the clinical context with isotretinoin and valproate were highlighted, particularly duration of treatment and population affected. Any PPP considered for valproate would need to be tailored specifically to the specific patient populations and the MHRA agreed to develop initial proposals to present to the Group at the next meeting.

7.10 NICE guidelines on epilepsy

The Group noted that the current NICE guidelines on epilepsy still positioned sodium valproate as a first line treatment for all patient populations, although the risks of valproate in women of childbearing potential was emphasised throughout. The Group discussed whether it would be helpful to have the recommendations in the NICE guidelines separated by age group and risk groups upfront. The Group agreed that NICE should be approached to further explore the current guidance on managing epilepsy.

7.11 The Group was asked if any Members were aware of any areas of best practice or countries with a particularly effective risk management system for sodium valproate. The Group discussed data from Ireland indicative of best practice in risk minimisation and noted that the UK and Ireland Epilepsy and Pregnancy Registry which is operated from Northern Ireland could partly explain the effective systems in place and the prominence of the issue there.

8. Need for Interim Measures pending outcome of EU Referral

The Group discussed paper 4.1 describing the regulatory action in France on 6 July 2017 to implement a contraindication for valproate use in bipolar disorder in women of child bearing potential not using effective contraception and was asked to consider the justification for interim regulatory action in the UK pending the outcome of the ongoing Referral in the EU. The Group considered tabled Paper I with written comments from Dr Leach.

8.1 The Group advised that they did not consider there is currently justification for implementing a contraindication for use of valproate in women of childbearing potential without effective contraception in either bipolar disorder or epilepsy pending the outcome of the EU Referral.

8.2 The Group noted that valproate was effectively contraindicated in women of childbearing potential in psychiatry practice and referred to the British Association of

Psychopharmacology guidelines.

8.3 The Group commented that for the epilepsy indication it would be very difficult to contraindicate in one specific subpopulation without other risk minimisation measures in place. Since there is recognised to be a small group of women who only respond to valproate, awareness of the risks should be reinforced, and ways suggested for additional risk minimisation including messaging about use of effective contraception reinforced.

8.4 The Group advised that pending the outcome of the EU Referral, the number of pregnancies exposed to sodium valproate should be monitored and the British and Irish Network of Congenital Anomaly Researchers(BINOCAR)was suggested as a registry that might help with collating these data.

9. Summary of action points

9.1 The next steps agreed at the meeting are summarized below.

1) GP software systems should be enhanced to ensure risk minimisation actions are taken when valproate is prescribed, including repeat prescription warnings, not just first prescriptions.
2) Shared-Care Arrangements for valproate should be explored with the relevant healthcare professional bodies.
3) The Quick Reference Guide issued by the Royal Pharmaceutical Society should be reviewed for potential updates.
4) Consideration should be given to drafting a CCPE module for pharmacists in liaison with the PNSC local Pharmaceutical Committee.
5) Communications from companies should be distributed to pharmacists rather than pharmacies by targeting Medicines Management Teams in each CCG.
6) A letter to GPs to help identify patients on valproate in need of neurology review will be considered by the ABN.
7) It should be considered how NICE guidance for managing epilepsy can be updated.
8) The impact of the NHSI/MHRA Patient Safety Alert on implementation of measures should be evaluated.
9) Proposals for a valproate specific PPP should be developed for discussion at the October meeting.
10) Exposed pregnancies should continue to be monitored through available data sources.

10. Any other Business

10.1 There was no other business.

11. Date and time of next meeting

11.1 It was agreed that Members and Invited Experts will meet again in October with 31st October the most likely date to be agreed.

ANNEX A

Declared interests by Chair, Members and Invited Experts

Chair	Interests declared
Professor Sir Munir Pirmohamed MB ChB (Hons) PhD FRCP FRCP (Edin) FBPhS FMedSci	I have not specifically worked on sodium valproate in relation to this issue, but some of the work that showed the effects of sodium valproate on cognitive outcomes after foetal drug exposure was undertaken by colleagues in the University of Liverpool (Baker and Bromley). Bromley has since moved onto another University while Baker has retired. However, I was not involved in any of the work. This did not debar the Chair from chairing this Working Group.
Members	
Professor J Helen Cross OBE MB ChB PhD FRCP FRCPCH	My department received an educational grant from Sanofi to fund a meeting January 2017. Note: The Chair ruled that this did not debar Professor Cross from taking part in the proceedings.
Dr Martin Duerden B Med Sci, MB BS, DRCOG, Dip Ther, DPH, FRCGP	None
Professor Jayne Lawrence	None
Dr Janine Lynch BHSCT	None
Dr Rebecca Mann BMBS FRCPCH	None

Dr Karen Miller BSc MBBS DRCOG DCH DFFP FRCGP	None
Professor Catherine Nelson-Piercy MBBSMA, FRCP, FRCOG	None
Dr Fergus Rugg-Gunn MB BS MRCP PhD	None
Ms Laura Russell	None
Professor Philip Smith	I have no product-specific interests in sodium valproate and have not undertaken research specifically on sodium valproate in isolation. However, I have participated in research that has involved sodium valproate alongside other antiepileptic medications: for example, I have randomised patients to the SANAD studies, which included sodium valproate as one of several randomised medications. I have not made any public commentary specifically on the safety of sodium valproate products. However, I give many lectures on epilepsy and included in these I will have described available research data on antiepileptic medication (including valproate). Also in the last 12 months I have been a member of the MHRA Valproate Stakeholders Group and so have made statements about sodium valproate in that forum. Note: The Chair ruled that this did not debar Professor Smith from taking part in the proceedings.
Mrs Madeleine Wang BA (Hons)	None
Invited Expert	
Professor Thomas R. E. Barnes MD FRCPsych DSc Professor of Clinical Psychiatry, Imperial College London	I have been a co-author of the following papers: James L, Paton C, Lelliott P, Barnes TRE, Taylor D. Mood stabilizers and teratogenicity-prescribing practice and awareness amongst practising psychiatrists Journal of Mental Health 2009;18:137–143. *This study attempted to evaluate the knowledge and stated practice of consultant psychiatrists with*

	respect to the prescribing of lithium, carbamazepine and valproate for women of child-bearing age. Semi-structured interviews were conducted with 52 consultant psychiatrists. Most prescribers (79–96%, depending on the drug) used these drugs and most (81–86%) were more cautious when prescribing to women of child-bearing age. Fewer (17–28%) demonstrated good, specific awareness of the estimated teratogenic potential of the individual drugs. Reported practice was characterized by reluctance to discuss contraception with patients, failure to prescribe prophylactic folate and uncertainty about who was clinically responsible for these issues. James L, Barnes TRE, Lelliott P, Taylor D, Paton C. Informing patients of the teratogenic potential of mood stabilizing drugs: a case note review of the practice of psychiatrists. Journal of Psychopharmacology 2007;21:815-819. *This paper reports on a review of clinical records of women of childbearing age, under the care of one specialist mental health Trust, who were prescribed lithium and/or carbamazepine and/or valproate. The findings related to documented discussion of the risks. Specifically, there was documented evidence indicating that just over 20% of these women had been informed about teratogenicity and nearly a quarter (24%) had been advised about contraception. Fourteen women (10%) had a confirmed pregnancy while taking lithium, carbamazepine or valproate; eight had a complication of pregnancy.* BALANCE investigators and collaborators, Geddes JR, Goodwin GM, Rendell J, Azorin JM, Cipriani A, Ostacher MJ, Morriss R, Alder N, Juszczak E. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. Lancet 2010;375:385-395. *I am one of 169 named collaborators on the BALANCE study, which was an open-label RCT of lithium monotherapy, valproate monotherapy, or both agents in combination for relapse prevention in bipolar I disorder. The conclusions from the findings were that for people with bipolar I disorder, for whom long-term therapy is clinically indicated, both combination therapy with lithium plus valproate and lithium monotherapy are more likely to prevent relapse than is valproate monotherapy. BALANCE could neither reliably confirm nor refute a benefit of combination therapy compared with lithium monotherapy.*

	I am co-clinical lead for the Prescribing Observatory for Mental Health (within the Centre for Quality Improvement at the Royal College of Psychiatrists) that issued the following report of a baseline clinical audit, part of a national quality improvement programme: Prescribing Observatory for Mental Health (2016). Topic 15a baseline audit report. Prescribing valproate for bipolar disorder. Prescribing Observatory for Mental Health, CCQI222 (data on file). In response to your query, I would not consider that the publications I mentioned in my personal interest declaration contain strong opinions for or against sodium valproate or the pharmaceutical companies. I have provided a brief summary of the papers, which may be helpful. Note: The Chair ruled that this did not debar Professor Barnes totake part in the proceedings as an invited expert.
External expert who provided expert advise via written procedure only	
Dr JP Leach	Review of Epilepsy management in pregnancy recommended actions for a range of healthcare professionals and patients – currently in epub but due publication imminently: (Epilepsy and Pregnancy: For healthy pregnancies and happy outcomes. Suggestions for service improvements from the Multispecialty UK Epilepsy Mortality Group. Seizure. 2017 Jun 1;50:67-72. doi: 10.1016/j.seizure.2017.05.004. [Epub ahead of print] Leach JP[1], Smith PE[2], Craig J[3], Bagary M[4], Cavanagh D[5], Duncan S[6], Kelso ARC[7], Marson AG[8], McCorry D[9], Nashef L[10], Nelson-Piercy C[11], Northridge R[12], Sieradzan K[13], Thangaratinam S[14], Walker M[15], Winterbottom J[16], Reuber M[17].) Also joint grant holder from HTA looking at use of valproate in newly diagnosed epilepsy – results awaited, recruitment finished. (SANAD2) Note: The Chair ruled that this did not debar Dr Leach from providing his expert advise via written procedure.

MEMBERSHIP OF THE SODIUM VALPROATE EXPERT WORKING GROUP

Chair

Professor Sir Munir Pirmohamed MB ChB (Hons) PhD FRCP FRCP (Edin) FBPhS FMedSci
David Weatherall Chair of Medicine, University of Liverpool, NHS Chair of Pharmacogenetics, Associate Executive Pro Vice Chancellor, Director of the Wolfson Centre for Personalised Medicine, Director of the MRC Centre for Drug Safety Science

Members

Professor J Helen Cross OBE MB ChB PhD FRCP FRCPCH
The Prince of Wales's Chair of Childhood Epilepsy, Deputy Head of Developmental Neurosciences Programme, UCL Institute of Child Health

Dr Martin Duerden B Med Sci, MB BS, DRCOG, Dip Ther, DPH, FRCGP
Member of National Stakeholder Platform, Honorary Senior Research Fellow, Centre for Health Economics and Medicines Evaluation, Bangor University

Dr Fergus Rugg-Gunn MB BS MRCP PhD
Consultant Neurologist, National Hospital for Neurology and Neurosurgery, Queen Square, London

Professor Philip Smith
Consultant Neurologist, Cardiff School of Medicine and former President of the Association of British Neurologists (ABN)

Professor Jayne Lawrence
Professor of Biophysical Pharmaceutics, Division of Pharmacy and Optometry, School of Health Sciences, Faculty of Biology, Medicine and Health, Manchester University and Visiting Professor of Biophysical Pharmaceutics, Institute of Pharmaceutical Science, King's College London

Dr Janine Lynch BHSCT
Psychiatrist, Belfast Health & Social Care Trust

Dr Rebecca Mann BMBS FRCPCH
Consultant Paediatrician, Taunton and Somerset NHS Foundation Trust

Dr Karen Miller BSc MBBS DRCOG DCH DFFP FRCGP
GP Partner, Adelaide Medical Centre, London

Professor Catherine Nelson-Piercy MBBSMA, FRCP, FRCOG
Professor of Obstetric Medicine and Consultant Obstetric Physician, Guy's & St Thomas' Foundation Trust

Ms Laura Russell
Senior Policy and Public Affairs Officer
Family Planning Association

Mrs Madeleine Wang BA (Hons)
Lay Representative. Patient Advocate
Invited experts

Professor Thomas R. E. Barnes MD FRCPsych DSc
Professor of Clinical Psychiatry, Imperial College London

NOT FOR PUBLICATION

COMMISSION ON HUMAN MEDICINES

SODIUM VALPROATE EXPERT WORKING GROUP

Minutes of the meeting held on Tuesday 31 October 2017 at 10am in R-T410 , 4th Floor, 151 Buckingham Palace Road, Victoria, London SW1W 9SZ

Members Present
Professor Sir M Pirmohamed (Chair)
Professor J H Cross*
Dr M Duerden
Professor J Lawrence
Dr J Lynch
Dr R Mann
Dr K Miller
Ms C Pelham
Dr F Rugg-Gunn
Ms L Russell
Professor P Smith
Mrs M Wang

Apologies
Professor C Nelson-Piercy

Invited Experts
Professor T Barnes

Secretariat
[redacted]

Professional Staff of MHRA Present
Principal Assessor
[redacted]

Supporting specific items
[redacted]

Others
[redacted]

* Participation from 10.50 during item 4.

1 Introductions, apologies and announcements

1.1 The Chair welcomed Ms Pelham as a new Member to the Group. All attending Members and Invited Experts introduced themselves.

1.2 The Group was notified of Members who had sent apologies. Apologies were received from Professor Nelson-Piercy.

1.3 The Chair reminded Members, Invited Experts and Observers that the papers and proceedings were confidential and should not be disclosed.

1.4 The Chair reminded Members and Invited Experts present to declare their personal specific, personal non-specific, non-personal specific and non-personal non-specific interests in the agenda items if they had not done so prior to the meeting.

Members were asked to declare interests in the associated companies, listed below, and any involvement with the product Sodium Valproate.

- Aventis
- Destin
- GL Pharma
- Noridem
- Norton
- Ratiopharm
- Teva
- Winthrop
- Wockhardt
- Sanofi
- Mylan
- Arrow Generiques/ Aurobindo
- Tecnifar
- Laboratoire Aguettant

1.5 The Chair directed participants to Tabled Paper I – written comments from Dr Leach and Tabled Paper II - written comments from Professor Nelson-Piercy and to Tabled Paper III - the register of interests declared by Chair, Members and Invited Experts, which was circulated to the Chair, Members and Invited experts in advance of the meeting.

1.6 Members' interests were reviewed against the Conflict of Interests Policy for the Sodium Valproate Expert Working Group and no potential conflicts were identified. All interests declared are listed at Annex A on page 8 to the minutes.

1.7 The Chair informed the Group that Professor Barnes was participating as an Invited Expert, and would be leaving the meeting room before the recommendations and final conclusions were discussed for items 4 and 5.

2 Minutes of the meeting held on the 2nd of August 2017

2.1 The draft minutes of the previous meeting held on 2nd August 2017 were discussed. Members requested that the minutes should be amended to clarify that the UKEPR

contained data from the Irish Republic as well as Northern Ireland, and the previous UCH prescription data related to valproate prescriptions by other specialists for psychiatry and neurology indications. With these changes, the minutes were adopted as an accurate account of the previous meeting of the SV-EWG.

3 Update on regulatory actions on valproate in pregnancy since the last meeting

3.1 A brief presentation summarised the key regulatory actions and significant data since the previous meeting. These included:

- The Public Hearing held on 26 September at the European Medicines Agency in the context of the European referral procedure
- Latest CPRD data showing little impact of regulatory action against a background of the overall declining trend in use that had started around 2010
- Educational material distribution metrics from the brand leader Marketing Authorisation holder
- Results from Epilepsy Society Survey showing, among other statistics, that 68% of women reported still not receiving the valproate toolkit

3.2 In particular the Group discussed the European Medicines Agency's (EMA's) Public Hearing, and advised that the issues raised by participants should be carefully considered. The Group noted the feedback from the Public Hearing that there continue to be issues with pharmacies in the UK not receiving toolkit materials, and the feedback from UK and Ireland that some women received their valproate dispensed in plain packaging without a patient information leaflet.

3.3 The Group asked for further information to be provided at the next meeting on the distribution of the valproate toolkit including a breakdown where, when and how many toolkits were distributed to try to assess the reasons for the complaints about lack of availability.

3.4 The Group noted feedback from GP members that although the NHS Improvement/MHRA Patient Safety Alert had been received by GPs and GP practices, it may not have been read or acted upon. As part of the alert procedure an audit report is being collated by NHSI.

4 EU Referral Rapporteurs' Assessment Report

4.1 Professor Barnes left the room before recommendations and final conclusions were discussed for this item.

4.2 MHRA summarised the Rapporteurs' assessment report for the ongoing EU Referral. The Group noted the current position of the Rapporteurs that there should be a contraindication for the use of valproate in pregnancy and in women without effective contraception for the bipolar disorder indication but not the epilepsy indication. The position of the UK will be informed by the EWG advice.

4.3 The Group discussed the need for a contraindication for the bipolar disorder indication and agreed that there was no situation under which it would be acceptable to initiate valproate in a patient who was already pregnant. Secondly, given the availability of alternative treatments for bipolar disorder, the Group supported a contraindication in

women of childbearing potential not using effective contraception. The Group discussed the practical implications of ensuring compliance with contraception given that patients treated with valproate for psychiatric indications often have changing mental capacity and ability to comply.

4.4 The Group discussed the clinical context of valproate treatment in the management of epilepsy, where a small group of women may not respond to other treatments and switching antiepileptic treatments had important clinical and lifestyle implications for patients. Nonetheless given the magnitude of risk to the fetus and lack of impact of lesser regulatory measures in achieving the goal of no exposed pregnancies, the Group advised that a contraindication in pregnant women and those of childbearing potential not taking effective contraception should also apply to the epilepsy indication. The Group discussed that a contraindication to the use of valproate in the treatment of women of child-bearing potential not on effective contraception would not prevent women from receiving valproate if it was considered the only effective treatment. The Group agreed that an appropriate, tailored 'pregnancy prevention programme' would ensure that female patients of child-bearing potential taking valproate were fully aware of the risks and the importance of effective contraception and were appropriately monitored. The Group discussed the situation of unintended pregnancy on valproate and advised that a decision on continuation would have to be made by the prescriber on consultation with the woman, after full discussion of the risks.

4.5 For the migraine indication, the Group noted that this was not a licensed indication in UK and that the previous European Referral had concluded that the benefit risk of valproate in the prophylaxis of migraine in women of child-bearing potential and in pregnant women was negative and such use was contraindicated The Group noted that there were several therapeutic alternatives. However, the Group advised that if valproate was prescribed off-label in the treatment or prophylaxis of migraine in women of child-bearing potential it should also be subject to the 'pregnancy prevention programme' requirements of the authorised indications.

4.5 The Group agreed that it would be important to clarify and clearly define the implications for patients of a contraindication to the use of valproate in pregnancy and in women of child-bearing potential not on effective contraception and that this should be addressed with key stakeholder groups including patient organisations.

4.7 The Group discussed the proposal made by the MAH during the EU Referral for a signed "acknowledgement" or "consent" form. The Group advised that obtaining a signature from the patient indicating that she had received and understood the information would be helpful in emphasising the importance of the risk minimisation measures and that a copy given to the patient as well as a copy retained within their medical notes would serve as a reminder that this discussion had taken place.

4.8 The Group discussed the importance of specialist oversight of valproate treatment in women of child-bearing potential and advised that the discussion on risks in pregnancy and the need for effective contraception should be undertaken annually, and the form signed, as part of an annual review of treatment with a specialist prescriber. The Group advised that the form could be called an Acknowledgement Form or Shared Decision Form and it should be supported with a formal Shared Care Agreement.

4.9 The Group discussed the need for a smaller pack size for valproate in the context of ongoing concerns that packs were being split at pharmacy level and the package warning and patient information leaflet were not reaching patients. The Group advised that a smaller pack size than the current which supported monthly prescribing intervals and delivery of regulatory information to women should be introduced.

4.10 The Group discussed the practicalities of identifying women of child-bearing potential already on long-term treatment with valproate many of whom have not had their treatment reviewed and ensuring that they were taking effective contraception. The Group also noted that 50% of girls under the age of 16 years are sexually active and they tended not to be on contraception and advised that consideration should be given to the most appropriate methods to discuss contraception with younger patients especially those already on valproate.

4.11 The Group advised that the clear call from patient organisations for a 'pictogram' on the outer packaging of valproate packs should be taken forward and that this should be supported by appropriate user testing. The Group asked that a clear timeline for implementation be provided to the members and urged that the user-testing exercise should be expedited.

5 Proposal for a bespoke valproate Pregnancy Prevention Programme

5.1 Professor Barnes left the room when recommendations and final conclusions were discussed for this item.

5.2 The Group discussed the key principles of a Pregnancy Prevention Programme for valproate, using the retinoid pregnancy prevention programme as a starting point. The Group discussed each of the key principles in turn.

5.3 *Contraception and Pregnancy Testing*
The Group advised that the need for, timing and frequency of pregnancy testing were dependent on the method of contraception used. The Group agreed that prescribers should use their clinical judgement to confirm that a monthly pregnancy test was not needed (e.g. that monthly testing would not be required in the case of women on user-independent long- acting contraception such as an implant or an IUD). Similarly, the requirement for effective contraception and pregnancy testing would not apply to females who were pre-pubertal or post-menarchal. The Group advised that monthly pregnancy testing for those women who needed it would not be expected to present an undue burden to the healthcare system, since the number of women in practice who would require monthly pregnancy tests would be very small.

5.4 The Group advised that approaches to implementing a bespoke Pregnancy Prevention Programme for valproate should be as flexible and supportive to patients as possible. Women with epilepsy should be encouraged to take responsibility and make an informed decision about their treatment, if valproate is clinically indicated.

5.5 The Group noted the results of a recent audit in which 2/3 of women on valproate for psychiatric indications had no contraception documented. The Group discussed the importance of referring patients to family planning services and specialist nurse support for advice on contraception and that there should be consideration of how to ensure that

patients are not put at risk in the time interval between seeing their specialist and obtaining effective contraception.

5.6 The Group advised that in the event of unintended pregnancy, a woman should see a specialist within days. The management of the pregnancy and the woman's treatment would then be based on a full discussion of the risks and benefits of each of the options with the woman.

5.7 *Pack size reduction*
The Group supported availability of smaller pack sizes to support monthly prescribing (para 3.8 above). The Group noted that a reduction in pack size would not be the same as limiting all prescriptions to a month's supply and multiple packs could be dispensed if longer prescription intervals were clinically indicated.

5.8 *Pictogram*
The Group advised that in principle it supported an appropriate pictogram for both the carton and foil blister if practical and subject to the advice of patient organisations.

5.9 The Group proposed that a bespoke Pregnancy Prevention Programme could include a requirement for entering women of child-bearing potential treated with valproate into a registry to help monitor compliance and any exposed pregnancies, and noted that MHRA should take forward discussions including with marketing authorisation holders as to how that could be implemented.

6 Software Updates

The Group supported the ongoing work with NHS Digital to improve the existing valproate alerts on GP prescribing systems and advised that this would be key to successful implementation of the new regulatory position.

7 Conclusion

The Chair summarised the advice of the Group which will be taken forward at national and EU level:

1) Valproate should be contraindicated in pregnancy and women of childbearing potential not using effective contraception
2) This should be supported by a bespoke 'Pregnancy Prevention Programme' for women of child-bearing potential who need valproate treatment with the requirement for pregnancy testing dependent on the method of contraception used, applicable to all indications and also in any off-label use
3) A signed 'acknowledgement' or 'consent' form should be routinely used when women are reviewed on an annual basis by a specialist in the context of shared care arrangements
4) A registry should be set up to record and track women taking valproate and monitor compliance with the Pregnancy Prevention Plan and any exposed pregnancies
5) Changes to GP prescribing systems to introduce alerts and information on the pregnancy prevention programme should be implemented to support these measures
6) Smaller pack sizes which support individual pack dispensing should be made available to ensure that warnings about use of valproate in pregnancy reach women

7) A pictogram, supported by appropriate user testing, should be introduced on valproate labelling as endorsed by patient organisations

7.1 The MHRA was asked promptly to take forward the following actions to be considered at the next meeting:

1) Prepare a summary of distribution metrics of the valproate toolkit, measures taken to ensure compliance with the regulatory position to date and an analysis of the reasons for the lack of impact
2) Prepare a detailed proposal for a bespoke valproate Pregnancy Prevention Programme including a patient registry
3) Work with GP software system providers to upgrade alerts for valproate on GP systems such that these support appropriate prescribing, regular annual review of women of child-bearing potential and the implementation of a bespoke valproate Pregnancy Prevention Programme.
4) Further progress the implementation of shared care arrangements for women of childbearing potential who need treatment with valproate
5) Prepare a strategy for communication of the new regulatory position together with key stakeholders.

The group concluded by emphasising the urgency of making progress with regulatory actions in light of (a) the available data on the extent of ongoing use of valproate in women of child-bearing potential; and (b) the survey evidence of the proportion of women who have not received information on the risks in pregnancy or advice on contraception.

8 Any other Business

8.1 There was no other business.

9. Date and time of next meeting

9.1 The next meeting of the Group is scheduled for Wednesday 31st of January 2017.

The meeting started at 10:05 AM and ended at 12:44 PM.

ANNEX A

Declared interests Chair, Members and Invited Experts

Chair	Interests declared 2nd of August meeting	New Interests declared 31st of October meeting
Professor Sir Munir Pirmohamed MB ChB (Hons) PhD FRCP FRCP (Edin) FBPhS FMedSci	I have not specifically worked on sodium valproate in relation to this issue, but some of the work that showed the effects of sodium valproate on cognitive outcomes after foetal drug exposure was undertaken by colleagues in the University of Liverpool (Baker and Bromley). Bromley has since moved onto another University while Baker has retired. However, I was not involved in any of the work. This did not debar the Chair from chairing this Working Group.	None
Members		
Professor J Helen Cross OBE MB ChB PhD FRCP FRCPCH	My department received an educational grant from Sanofi to fund a meeting January 2017. Note: The Chair ruled that this did not debar Professor Cross from taking part in the proceedings.	My institution has received an educational grant for a research event from Sanofi.
Dr Martin Duerden B Med Sci, MB BS, DRCOG, Dip Ther, DPH, FRCGP	None	None
Professor Jayne Lawrence	None	None

Dr Janine Lynch BHSCT	None	
Dr Rebecca Mann BMBS FRCPCH	None	None
Dr Karen Miller BSc MBBS DRCOG DCH DFFP FRCGP	None	None
Professor Catherine Nelson-Piercy MBBSMA, FRCP, FRCOG	None	None
Ms Clare Pelham	Not a Member at this date	I am not aware of any non-personal interests but I have asked for checks to be made within Epilepsy Society. I have not personally conducted any reviews of Sodium valproate or research. I am not aware of any product-specific interests of the Epilepsy Society, but I have asked for checks to be made and this information will follow. I have commented publicly on the desirability of information about risk during pregnancy being provided more regularly and comprehensively to woman and girls of childbearing age who have been prescribed Sodium Valproate. As I said on the completed form, the information relating to the Epilepsy Society will follow as soon as we are able to compile it. It may be helpful to note that I became Chief Executive here on 14 November 2016, and, as I said on the

		form, I am not personally aware of any non-personal interests or product-specific interests of the Epilepsy Society. I have never expressed any strong opinions on the merits or otherwise of the drug, sodium valproate, to the best of my recollection. My comments have focused on the provision of information.
Dr Fergus Rugg-Gunn MB BS MRCP PhD	None	None
Ms Laura Russell	None	None
Professor Philip Smith	I have no product-specific interests in sodium valproate and have not undertaken research specifically on sodium valproate in isolation. However, I have participated in research that has involved sodium valproate alongside other antiepileptic medications: for example, I have randomised patients to the SANAD studies, which included sodium valproate as one of several randomised medications. I have not made any public commentary specifically on the safety of sodium valproate products. However, I give many lectures on epilepsy and included in these I will have described available research data on antiepileptic medication (including valproate). Also in the last 12 months I have been a member of the MHRA Valproate Stakeholders Group and so have made statements about sodium valproate in that forum. Note: The Chair ruled that this did not debar Professor Smith from taking part in the proceedings.	

Mrs Madeleine Wang BA (Hons)	None	None
Invited Expert		
Professor Thomas R. E. Barnes MD FRCPsych DSc Professor of Clinical Psychiatry, Imperial College London	I have been a co-author of the following papers: James L, Paton C, Lelliott P, Barnes TRE, Taylor D. Mood stabilizers and teratogenicity-prescribing practice and awareness amongst practising psychiatrists Journal of Mental Health 2009;18:137–143. *This study attempted to evaluate the knowledge and stated practice of consultant psychiatrists with respect to the prescribing of lithium, carbamazepine and valproate for women of child-bearing age. Semi-structured interviews were conducted with 52 consultant psychiatrists. Most prescribers (79–96%, depending on the drug) used these drugs and most (81–86%) were more cautious when prescribing to women of child-bearing age. Fewer (17–28%) demonstrated good, specific awareness of the estimated teratogenic potential of the individual drugs. Reported practice was characterized by reluctance to discuss contraception with patients, failure to prescribe prophylactic folate and uncertainty about who was clinically responsible for these issues.* James L, Barnes TRE, Lelliott P, Taylor D, Paton C. Informing patients of the teratogenic potential of mood stabilizing drugs: a case note review of the practice of psychiatrists. Journal of Psychopharmacology 2007;21:815-819. *This paper reports on a review of clinical records of*	None

	women of childbearing age, under the care of one specialist mental health Trust, who were prescribed lithium and/or carbamazepine and/or valproate. The findings related to documented discussion of the risks. Specifically, there was documented evidence indicating that just over 20% of these women had been informed about teratogenicity and nearly a quarter (24%) had been advised about contraception. Fourteen women (10%) had a confirmed pregnancy while taking lithium, carbamazepine or valproate; eight had a complication of pregnancy. BALANCE investigators and collaborators, Geddes JR, Goodwin GM, Rendell J, Azorin JM, Cipriani A, Ostacher MJ, Morriss R, Alder N, Juszczak E. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. Lancet 2010;375:385-395. *I am one of 169 named collaborators on the BALANCE study, which was an open-label RCT of lithium monotherapy, valproate monotherapy, or both agents in combination for relapse prevention in bipolar I disorder. The conclusions from the findings were that for people with bipolar I disorder, for whom long-term therapy is clinically indicated, both combination therapy with lithium plus valproate and lithium monotherapy are more likely to prevent relapse than is valproate monotherapy. BALANCE could neither reliably confirm nor refute a benefit of combination therapy compared with lithium monotherapy.*	

	I am co-clinical lead for the Prescribing Observatory for Mental Health (within the Centre for Quality Improvement at the Royal College of Psychiatrists) that issued the following report of a baseline clinical audit, part of a national quality improvement programme: Prescribing Observatory for Mental Health (2016). Topic 15a baseline audit report. Prescribing valproate for bipolar disorder. Prescribing Observatory for Mental Health, CCQI222 (data on file). In response to your query, I would not consider that the publications I mentioned in my personal interest declaration contain strong opinions for or against sodium valproate or the pharmaceutical companies. I have provided a brief summary of the papers, which may be helpful. Note: The Chair ruled that this did not debar Professor Barnes totake part in the proceedings as an invited expert.	
External expert who provided expert advise via written procedure only		
Dr JP Leach	Review of Epilepsy management in pregnancy recommended actions for a range of healthcare professionals and patients – currently in epub but due publication imminently: (Epilepsy and Pregnancy: For healthy pregnancies and happy outcomes. Suggestions for service improvements from the Multispecialty UK Epilepsy Mortality Group. Seizure. 2017 Jun	None

	1;50:67-72. doi: 10.1016/j.seizure.2017.05.004. [Epub ahead of print] Leach JP[1], Smith PE[2], Craig J[3], Bagary M[4], Cavanagh D[5], Duncan S[6], Kelso ARC[7], Marson AG[8], McCorry D[9], Nashef L[10], Nelson-Piercy C[11], Northridge R[12], Sieradzan K[13], Thangaratinam S[14], Walker M[15], Winterbottom J[16], Reuber M[17].) Also joint grant holder from HTA looking at use of valproate in newly diagnosed epilepsy – results awaited, recruitment finished. (SANAD2) Note: The Chair ruled that this did not debar Dr Leach from providing his expert advice via written procedure.	

NOT FOR PUBLICATION

COMMISSION ON HUMAN MEDICINES

Minutes of the meeting held on Thursday 7th & Friday 8th December 2017 at 10am in R-T-501-503, 5th Floor, 151 Buckingham Palace Road, Victoria, SW1W 9SZ

Commissioners Present

Professor S H Ralston (Chair)
Dr J C Forfar
*1 Dr J Fraser
Professor J S Friedland
Dr R J C Gilson
Professor M Gore
Professor M R Macleod
Dr R J Mann
Professor S Meredith
*2 Dr S Misbah
Professor D G C Owens
Professor Sir Munir Pirmohamed
*3 Professor S Price
Professor K M G Taylor
Professor A E Thomas
Professor H M Ward
Professor C Weir

Apologies

Dr M Wilson

Invited Experts

*4 Professor M Bellamy
*5 Dr Peter Nightingale
*6 Professor Jerry Nolan
Mrs Madeleine Wang

Secretariat

[redacted]

Observers

Dr Krithika Murali *(Thursday only)*

MHRA Legal on call

[redacted] *(Thursday am)*
[redacted] *(Thursday pm)*
[redacted] *(Friday am)*

Professional Staff of MHRA Present

Principal Assessors **Item**

[redacted]

Licensing

[redacted]

*1 *Attended on Friday only*
*2 *Left at 3pm on Thursday*
*3 *Thursday: arrived at 11:30 during item 7*
*4 *Dialled in at 10:12 during item 2.1*
*5 *Attended for items 2.1 and 3.1*
*6 *Dialled in for item 2.1*

VRMM

Others

3.1.2 [redacted]

3.1.3 [redacted]

4. Paper

4.1	**Sodium Valproate: risks in pregnancy**	**Multiple, including: Sanofi, Destine Pharma, Wockhardt, Zentiva, Aguettant, Actavis, Gerot Lannach, TAD, GES and Genfarma**

4.1.1 The following Commissioners declared non-personal, non-specific interests, however this did not debar them from taking part in proceedings:

- Dr Gilson – Mylan
- Professor Macleod – Sanofi
- Professor Meredith – Sanofi

4.1.2 The Commission noted Tabled Papers VI and VIII.

4.1.3 The Commission considered a paper for information summarising the discussions at the second meeting of the Sodium Valproate – Expert Working Group (SV- EWG) held on 31 October. The draft minutes of the meeting were tabled.

4.1.4 The Commission noted that following consideration of the available data the SV-EWG recommended a contraindication for use of valproate in women of childbearing potential not using effective contraception for bipolar disorder and epilepsy and that any essential use in women of childbearing potential should be supported by an appropriate pregnancy prevention program (PPP).

4.1.5 The Commission noted the concern raised during the SV-EWG meeting and at the Pharmacovigilance Risk Assessment Committee (PRAC) of unplanned pregnancy management and the PRAC agreed caveat for use in pregnancy, “unless there are no suitable alternatives”.

4.1.6 The Commission welcomed the strengthened regulatory position. The Commission advised that clear prescribing protocols should be developed with specialists and that these should be used in measuring the effectiveness of the PPP implementation. The Commission noted that the role of patients and pharmacists in designing the PPP will be crucial.

4.1.7 The Commission discussed the use of a “consent” or acknowledgement form to record the annual discussions that will form part of the PPP and recommended

that the form should be available in three copies - one kept by the specialist, one for the patient and one sent to their GP.

4.1.8 The Commission noted that capacity to consent may be impaired in patients with bipolar disorder and learning disability and that poor compliance with user dependent methods of contraception should be taken into account when developing the PPP.

4.1.9 The Commission noted that the psychiatry Scientific Advice Group (SAG) had especially welcomed the contraindication in bipolar disorder and considered it somewhat overdue. In psychiatry, there are several alternatives to valproate including lithium but the prescribing of valproate to women of child bearing potential continues and there is great variation in clinical practice across Europe.

4.1.10 The Commission noted the limitations in current CPRD data regarding pregnancy outcomes (live births vs. still births and spontaneous abortion) and called for better data to be made available.

4.1.11 The Commission noted that the number of patients with idiopathic generalised epilepsy in whom only valproate is effective is uncertain but acknowledged that it may be difficult to switch antiepileptic medication for multiple reasons including the harm associated with other antiepileptic drugs which could be as high as valproate or not known. The Commission supported the PPP but requested that provisions should be made within the PPP for unplanned pregnancies as well as women who may want to become pregnant despite being fully informed of the known risks.

4.1.12 The Commission noted ongoing work to update NICE guidelines in epilepsy and enhance prescribing software to better support the message of the PPP.

4.1.13 The Commission noted that the PRAC position is likely to be finalised in February 2018. Progress of the ongoing work streams informed by input from the valproate stakeholder network and SV-EWG will be discussed at the next SV-EWG meeting to be held at the end of January.

5. Minutes of the meeting held on Thursday 2nd & 3rd November 2017

5.1 Minutes

5.1.1 The minutes were signed as a true and accurate record of the proceedings, subject to minor amendments.

5.2 Website Minutes

5.2.1 The website minutes were approved for publication, subject to minor amendments.

NOT FOR PUBLICATION

COMMISSION ON HUMAN MEDICINES

SODIUM VALPROATE EXPERT WORKING GROUP

Minutes of the meeting held on Thursday 29 March 2018 at 10:30am in R-T-501/502, 5th Floor, 151 Buckingham Palace Road, Victoria, London SW1W 9SZ

Members Present

Professor Sir M Pirmohamed (Chair)
[1] Professor J H Cross*
Dr M Duerden
Professor J Lawrence
Dr J P Leach
Dr J Lynch
[2] Professor D G C Owens
Ms C Pelham
Dr F Rugg-Gunn
Professor P Smith

Invited Experts

Professor T Barnes

Visiting Experts

Ms J Ashton
Ms E Murphy
Ms J Williams

Apologies

Professor C Nelson-Piercy
Dr R Mann
Dr K Miller
Mrs M Wang

Professional Staff of MHRA Present

Principal Assessor

[redacted]

Supporting specific items

[redacted]

Secretariat

[redacted]

17/5/18

[1] *arrived during item 5.1*

[2] *left during item 5.3*

1. Introductions, apologies and announcements

1.1 The Chair welcomed to group to its 4th meeting. The Chair reminded Members, Invited Experts and Observers that the papers and proceedings were confidential and should not be disclosed.

1.2 Apologies were received from:

- Professor C Nelson-Piercy
- Dr R Mann
- Dr K Miller
- Mrs M Wang

1.3 The Chair welcomed:

- **Ms Juliet Ashton**
  Adult Epilepsy Specialist Nurse, Dereham Hospital
- **Ms Emma Murphy** and **Ms Janet Williams**
  Independent Fetal Anti-Convulsant Trust (INFACT)

who attended as an Invited Experts for the meeting.

1.4 The Chair reminded Members and Invited Experts present to declare their personal specific, personal non-specific, non-personal specific and non-personal non-specific interests in the agenda items if they had not done so prior to the meeting. Members were asked to declare interests in the associated companies, listed below, and any involvement with the product Sodium Valproate.

- Aventis
- Destin
- GL Pharma
- Noridem
- Norton
- Ratiopharm
- Teva
- Winthrop
- Wockhardt
- Sanofi
- Mylan
- Arrow Generiques/ Aurobindo
- Tecnifar
- Laboratoire Aguettant
- Actavis (owned by Teva)
- Gerot Lannach
- Genfarma
- TAD Pharma GmbH
- GES Group, now owned by Altan Pharma Ltd
- Pfizer
- Zentiva

1.4.1 All interests declared are listed at **Annex A** (page 9) to the minutes, members and invited experts declared no interests in the companies at the meeting.

2 Minutes of the meeting held on the 31st January 2018

2.1 The minutes were signed as a true and accurate record of the proceedings, subject to minor amendments.

2.2 An action register was requested to clearly outline target dates for completion of action points and accountability. This will be further discussed by MHRA Secretariat and feedback provided to the Group. The action register is attached as **Annex B** (page 16) to the minutes.

3. Matters Arising

3.1 There were no matters arising.

4. Papers for Information

4.1 Risk of Paternal and Transgenerational transmission of developmental disorders

4.1.1 The Group heard about the plans for ongoing EU work on paternal and transgenerational transmission of valproate risks. MHRA said that they would put forward UK experts for the expert panel which was being organised by the EMA and would keep the Group informed of progress. The Group advised that this was a complex issue requiring specialist expertise. The Group advised that it would be important to consider that the lower end of the dose response curve for epigenetic changes in sperm was unknown. The Group advised that the follow up period for children in the real world studies should be extended as the symptoms exhibited by those affected by fetal valproate syndrome were different at different ages.

5. Implementation of the outcome of the referral – for advice

5.1 Update on final referral outcome

5.1.1 The Group considered the changes to the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) which had been agreed as part of the referral and were presented for information. The Group noted that a number of points made on wording of the SmPC and PIL at the previous meeting were not fully reflected in the final versions. MHRA said that the drafting of the changes at EU level necessarily meant that there was compromise on some aspects of the wording in the final regulatory documents; however the wording of the educational materials was for national agreement and therefore these could be amended to ensure clarity as long as they remained consistent with the regulatory position.

5.1.2 The Group commented that the PIL did not reflect that the information may be important for a parent or carer in addition to the patient themselves. MHRA said that there was some flexibility about national changes to the PIL and that this point would be further explored.

5.2 Educational materials

5.2.1 Risk Acknowledgment Form

5.2.1.1 The Group discussed the draft Risk Acknowledgement Form. The Group advised that the advice of behavioural insight experts within the Department of Health and Social Care should be sought on the form as they had expertise in the best way to design forms to engage the audience. MHRA said that they would look into this. The Group felt that the form would benefit from editorial review to improve the consistency (patient versus female, childbearing potential versus childbearing age) and flow of the language used and aid readability. Simple words should be used where possible (eg 'starting' rather than 'initiation'). The Group advised that the word 'must' should be used instead of 'should' consistently throughout the educational materials. The Group advised that the readability of the materials for those with learning difficulties should be addressed. The Group advised that the MHRA should seek legal advice on the terminology used for the person taking decisions where the patient lacked capacity (responsible person versus caregiver). The Group advised that there should be an update/renewal date on the acknowledgement form to make clear when the form expired and to prompt the patient to make an appointment to have their treatment reviewed.

5.2.2 Health Professional Guide

5.2.2.1 The Group discussed the draft healthcare professional guide. The Group advised that the guide should be very explicit as to exactly what the PPP entailed. The Group asked about the omission of advice on the use of folate. MHRA explained that this was not included as while there was evidence that folate reduced the background rate of abnormalities, the evidence considered at the time of the referral suggested that it did not mitigate valproate specific risks and therefore to include information on folate was considered to be falsely reassuring. The Group advised that new data had been published on the effectiveness of folate on valproate specific risks and that in any case there should be mention about the need for women to take measures to be healthy in pregnancy, including folate.

5.2.2.2 The Group advised that the healthcare professional guide should be more specific about the description of highly effective contraception. The Group advised that GPs were key to the successful implementation of the measures and most had an interest in family planning and would be well placed and motivated to deliver their responsibilities as part of the PPP. The Group noted however that family planning had moved to the control of the local authorities in 2014 and this meant the availability of family planning was variable throughout the country. The Group advised that pivotal to the success of the implementation was a formal shared care agreement outlining the roles and responsibilities (clinical and legal) of primary and secondary care and that this should be developed through the RCGP. GPs would require a letter from the specialist formally handing over the patient's care to the GP and the letter would need to be explicit about how the GP should monitor the patient's treatment. The Group discussed use of paper forms versus electronic

availability and noted that hospitals were at different stages in terms of moving to electronic prescribing systems.

5.2.2.3 The Group noted that epilepsy nurse specialists provided preconception counselling and were based in the community and had an important role to play. The Group discussed whether a QOF could be re-established but noted that QOFs were now managed by NICE and there were regional variations. The Group advised that introducing a CQUIN indicator for valproate prescribing should be considered by NHSE.

5.2.2.4 The Group raised the question of who would pay for the pregnancy tests required by the PPP and that the cost of pregnancy tests to women must not be underestimated. The Group noted that SPC specified that there should be a plasma pregnancy test before initiation of valproate and that this would be conducted in secondary care.

5.2.2.5 The Group considered the role of the pharmacist and the importance of including key messages about valproate dispensing in pharmacy education. The Group noted that the MHRA was in discussion with the Royal Pharmaceutical Society and advised that there was a need to ensure that any valproate guidance was included in the part of the website that was open to all, and not just to RPS members. The Group advised that the MHRA should contact the General Pharmaceutical Council and discuss their role in ensuring good practice.

5.2.2.6 The Group asked about progress with the advice from the last meeting about making an uninformed pregnancy on valproate a "never event". MHRA said that this had been raised with NHS Improvement and that the Group would receive feedback.

5.2.2.7 The issue of informed choice to plan a pregnancy while taking valproate was raised and the Chair allowed discussion of the various clinical and patient perspectives on this issue. The Group heard that from one neurology perspective, if a woman had capacity to make the decision, had tried other treatment options and had had discussions on more than one occasion about the risks (including discussions with family members as appropriate) then she should be able to make the decision to plan a pregnancy with a modified treatment regimen that could include reduction of the valproate dose. Another neurology viewpoint was that it would be impossible to ensure that a woman fully understood the magnitude of the risk and the impact on her family of having a baby exposed to valproate.

5.2.2.8 From a psychiatry perspective, the Group heard that mood stabilisation could always be achieved with other agents but many patients were on valproate because prescribers were concerned about the side effects of lithium. There was a culture within psychiatry of not wanting to rock the boat and concern was expressed that a message that planning a pregnancy on valproate was acceptable would undermine the strengthened regulatory position.

5.2.2.9 From a patient perspective, the Group heard that there had been cases of children affected whose mothers had taken a very low dose during pregnancy and therefore it was important that women were not given false reassurance about the effect of lowering the dose on the risks of valproate in pregnancy. It was not clear how to ensure that women were truly informed of the impact on them and their families of having a child affected by valproate. There was a concern that many women who wanted children would think that the risks did not apply to them. The Group advised that there needed to be a support network for women. The Chair raised the issue of the child's perspective and asked if a child with brain damage due to valproate use in pregnancy could take legal action against the mother who had made an informed choice. One member raised the need to consider faith groups for whom contraception is not an option.

5.2.3 Patient guide

5.2.3.1 The Group discussed the patient guide and advised that it was generally good although there should be a check across all materials to ensure consistency of language. MHRA was asked to circulate word versions of the materials discussed and the patient card for written comments after the meeting.

5.2.3.2 The Group discussed the branding of the materials and raised concern that any materials sent out by the marketing authorisation holder (MAH) would not be viewed as official government materials. The Group commented that such an important public health message should be delivered through government produced materials. MHRA said that the MAHs had a legal obligation to produce materials to support the safe use of their product and that the MHRA had control over the content of the materials, which would carry the MHRA/government logo. In addition, MHRA was working with NICE and NHS Digital to ensure that there would be consistent messages across the healthcare system including at the point of care in GP prescribing systems.

5.2.3.3 The Group commented on the audience for distribution of the materials (tabled paper III) and advised that acute medicine should be included, and the pharmacy network contacted to ensure consistent messaging. MHRA was asked whether the materials would be distributed to healthcare professionals in hard copy and confirmed that they would. MHRA said that the CQC role included compliance with the valproate resource alert sent in 2017 and would have a role in the new action.

5.3 Implementation and Communication Plan

5.3.1 The Group heard a presentation on the draft communications plan to support the implementation. The slide is attached as **Annex C** (page 18) to the minutes.
The Group advised that it was extremely important to get the communications right and to demonstrate learning from the lack of impact of the communications following the previous referral. The question was raised as to whether the proposed communication date of April 17th was realistic given the need to finalise plans and materials. One member asked about the MHRA budget to support the communications and was informed that the plan would be supported by the engagement, marketing and press teams from MHRA's Communications division. The Group noted that charities were highly regulated and there are restrictions on charities being used to conduct communications that would otherwise be undertaken by public services. The Group advised that the communications to the public through the media were extremely important and that this should be more explicit in the plan. The Group recommended that the Epilepsy Nurse Specialists network and the Royal College of Nursing should both be included in the Valproate Stakeholders' Network (VSN). This would further increase the reach to relevant healthcare professionals that can be achieved though the supportive communications to be issued by the organisations in the VSN. The
The VSN list of actions committed to support implementation of the new measures March 2018 is attached as **Annex D** (page 30) to the minutes.

5.4 Studies to monitor the impact of new risk minimisation measures

5.4.1 The Group heard a presentation on the range of plans being put in place for monitoring the impact of the new risk minimisation measures on a national basis. The slide is attached as **Annex E** (page 34) to the minutes The Group were also presented with data up to December 2017 from the Clinical Practice Research Datalink (CPRD) on the prescribing of valproate in the UK. The Group advised that monitoring outcomes was very important and agreed that multiple approaches would be required in order to understand the wider impact of the new measures.

5.4.2 From a paediatric neurology perspective, the Group advised that prescribing of valproate would likely increasingly move back to specialist care. The Epilepsy 12 national audit was highlighted as a potential additional route for gathering relevant data. MHRA agreed to follow up with the Royal College of Paediatrics and Child Health project team to assess how this audit could support the monitoring of the impact of the new measures. The Group also advised it would be important to monitor for unintended events such as a rise in hospital admissions due to uncontrolled epilepsy.

5.4.3 The Group highlighted the previous national audit conducted by the Prescribing Observatory for Mental Health within UK specialist mental health services which included measures on the prescribing of valproate and advised that this was due to be repeated in two years.

5.4.4 In the context of the proposed registry, the Group advised that the Risk Acknowledgement Form should include a section on what the patient's data would be used for and a box should be added for patients to tick to give their permission for the information to be included in the registry. The Group advised that legal advice should be sought on this point. The Group advised that having a SNOMED CT code for recording completion of the Risk Acknowledgement Form would facilitate monitoring. The Group also asked if the registry could be made mandatory.

5.4.5 The Group noted the audit function that would be available within GP clinical systems software to allow GPs to identify women of child bearing age prescribed valproate within their practice. MHRA said they would ask NHS Digital if data could be captured on the use of this tool.

5.4.6 The Group discussed the use of patient surveys to monitor levels of awareness of the new measures and asked about the potential for MHRA to make funding available for charity organisations to conduct further surveys. MHRA said that they would consider the availability for funding and would be able to work with charities on the surveys to address resource concerns.

6 Next steps

6.1 Timelines for next steps is attached as **Annex F** (page 43) to the minutes)

7 Any other Business

7.1 The Group heard about the establishment of a review to be led by Baroness Julia Cumberlege into how to improve the way the healthcare system hears and responds to patient-reported concerns. The Group noted that this review was set up in response to concerns about vaginal mesh, valproate and hormone pregnancy tests and asked that there was an agenda item at the next meeting so that the Group could reflect on the review.

8. Date and time of next meeting

8.1 The next meeting of the Group is scheduled for Thursday 17th May 2018.

*The meeting started at 10:33am and ended at 13:15

ANNEX A

Declared interests Chair, Members and Invited Experts

SODIUM VALPROATE EXPERT WORKING GROUP

Register of Interests Declared by Members and Invited Experts

Chair	Interests declared up to 31st January 2018 meeting	New Interests declared 29th March 2018 meeting	Action The meeting focussed on issues of implementation and communication rather than regulatory decisions
Professor Sir Munir Pirmohamed MB ChB (Hons) PhD FRCP FRCP (Edin) FBPhS FMedSci	I have not specifically worked on sodium valproate in relation to this issue, but some of the work that showed the effects of sodium valproate on cognitive outcomes after foetal drug exposure was undertaken by colleagues in the University of Liverpool (Baker and Bromley). Bromley has since moved onto another University while Baker has retired. However, I was not involved in any of the work. This did not debar the Chair from chairing this Working Group.		None
Members			
Professor J Helen Cross OBE MB ChB PhD FRCP FRCPCH	My department received an educational grant from Sanofi to fund a meeting January 2017. My institution has received an educational grant for a research event from Sanofi.	Our department has received educational grants from	None

	Note: The Chair ruled that this did not debar Professor Cross from taking part in the proceedings.	Sanofi and Desitin	
Dr Martin Duerden B Med Sci, MB BS, DRCOG, Dip Ther, DPH, FRCGP	None	None	None
Professor Jayne Lawrence	None	None	None
Dr John Paul Leach	Review of Epilepsy management in pregnancy recommended actions for a range of healthcare professionals and patients – currently in epub but due publication imminently: (Epilepsy and Pregnancy: For healthy pregnancies and happy outcomes. Suggestions for service improvements from the Multispecialty UK Epilepsy Mortality Group. Seizure. 2017 Jun 1;50:67-72. doi: 10.1016/j.seizure.2017.05.004. [Epub ahead of print] Leach JP[1], Smith PE[2], Craig J[3], Bagary M[4], Cavanagh D[5], Duncan S[6], Kelso ARC[7], Marson AG[8], McCorry D[9], Nashef L[10], Nelson-Piercy C[11], Northridge R[12], Sieradzan K[13], Thangaratinam S[14], Walker M[15], Winterbottom J[16], Reuber M[17].) Also joint grant holder from HTA looking at use of valproate in newly diagnosed epilepsy – results awaited, recruitment finished. (SANAD2) **Note**: The Chair ruled that this did not debar Dr Leach from taking part in the proceedings.		None
Dr Janine Lynch BHSCT			
Dr Rebecca Mann BMBS FRCPCH	None		None

Dr Karen Miller BSc MBBS DRCOG DCH DFFP FRCGP	None		None
Professor Catherine Nelson-Piercy MBBSMA, FRCP, FRCOG	None		None
Professor David G C Owens MD (Hons) FRCP FRCPsych	NP-NS - Proposal from EMA to collaborate with secretariat for a publication on psychiatric literature		None
Ms Clare Pelham	I am not aware of any non-personal interests but I have asked for checks to be made within Epilepsy Society. I have not personally conducted any reviews of Sodium valproate or research. I am not aware of any product-specific interests of the Epilepsy Society, but I have asked for checks to be made and this information will follow. I have commented publicly on the desirability of information about risk during pregnancy being provided more regularly and comprehensively to woman and girls of childbearing age who have been prescribed Sodium Valproate. As I said on the completed form, the information relating to the Epilepsy Society will follow as soon as we are able to compile it. It may be helpful to note that I became Chief Executive here on 14 November 2016, and, as I said on the form, I am not personally aware of any non-personal interests or product-specific interests of the Epilepsy Society. I have never expressed any strong opinions on the merits or otherwise of the drug, sodium valproate, to the best of my recollection. My comments have focused on the provision of information.		None
Dr Fergus Rugg-Gunn MB BS MRCP PhD	None	None	None

Ms Laura Russell	None (left the Group)		None
Professor Philip Smith	I have no product-specific interests in sodium valproate and have not undertaken research specifically on sodium valproate in isolation. However, I have participated in research that has involved sodium valproate alongside other antiepileptic medications: for example, I have randomised patients to the SANAD studies, which included sodium valproate as one of several randomised medications. I have not made any public commentary specifically on the safety of sodium valproate products. However, I give many lectures on epilepsy and included in these I will have described available research data on antiepileptic medication (including valproate). Also in the last 12 months I have been a member of the MHRA Valproate Stakeholders Group and so have made statements about sodium valproate in that forum. Note: The Chair ruled that this did not debar Professor Smith from taking part in the proceedings.		None
Mrs Madeleine Wang BA (Hons)	None		None
Invited Expert			
Professor Thomas R. E. Barnes MD FRCPsych DSc Professor of Clinical Psychiatry, Imperial College London	I have been a co-author of the following papers: James L, Paton C, Lelliott P, Barnes TRE, Taylor D. Mood stabilizers and teratogenicity-prescribing practice and awareness amongst practising psychiatrists Journal of Mental Health 2009;18:137–143. *This study attempted to evaluate the knowledge and stated practice of consultant psychiatrists with respect to*	None	Restricted participation at second meeting by answering specific questions from the Chair only. Will not be able to attend and participate in the final discussion section

	the prescribing of lithium, carbamazepine and valproate for women of child-bearing age. Semi-structured interviews were conducted with 52 consultant psychiatrists. Most prescribers (79–96%, depending on the drug) used these drugs and most (81–86%) were more cautious when prescribing to women of child-bearing age. Fewer (17–28%) demonstrated good, specific awareness of the estimated teratogenic potential of the individual drugs. Reported practice was characterized by reluctance to discuss contraception with patients, failure to prescribe prophylactic folate and uncertainty about who was clinically responsible for these issues. James L, Barnes TRE, Lelliott P, Taylor D, Paton C. Informing patients of the teratogenic potential of mood stabilizing drugs: a case note review of the practice of psychiatrists. Journal of Psychopharmacology 2007;21:815-819. *This paper reports on a review of clinical records of women of childbearing age, under the care of one specialist mental health Trust, who were prescribed lithium and/or carbamazepine and/or valproate. The findings related to documented discussion of the risks. Specifically, there was documented evidence indicating that just over 20% of these women had been informed about teratogenicity and nearly a quarter (24%) had been advised about contraception. Fourteen women (10%) had a confirmed pregnancy while taking lithium, carbamazepine or valproate; eight had a complication of pregnancy.* BALANCE investigators and collaborators, Geddes JR, Goodwin GM, Rendell J, Azorin JM, Cipriani A, Ostacher MJ, Morriss R, Alder N, Juszczak E. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder		and recommendations. He will be asked to leave the room when reaching the conclusions. This will be for items 4.1 and 4.2 at the meeting.

	(BALANCE): a randomised open-label trial. Lancet 2010;375:385-395. *I am one of 169 named collaborators on the BALANCE study, which was an open-label RCT of lithium monotherapy, valproate monotherapy, or both agents in combination for relapse prevention in bipolar I disorder. The conclusions from the findings were that for people with bipolar I disorder, for whom long-term therapy is clinically indicated, both combination therapy with lithium plus valproate and lithium monotherapy are more likely to prevent relapse than is valproate monotherapy. BALANCE could neither reliably confirm nor refute a benefit of combination therapy compared with lithium monotherapy.* I am co-clinical lead for the Prescribing Observatory for Mental Health (within the Centre for Quality Improvement at the Royal College of Psychiatrists) that issued the following report of a baseline clinical audit, part of a national quality improvement programme: Prescribing Observatory for Mental Health (2016). Topic 15a baseline audit report. Prescribing valproate for bipolar disorder. Prescribing Observatory for Mental Health, CCQI222 (data on file). In response to your query, I would not consider that the publications I mentioned in my personal interest declaration contain strong opinions for or against sodium valproate or the pharmaceutical companies. I have provided a brief summary of the papers, which may be helpful. Note: The Chair ruled that this did not debar Professor Barnes to take part in the proceedings as an invited expert.		

Visiting Experts		Interests declared up to 29th March 2018 meeting	
Ms Juliet Ashton Adult Epilepsy Specialist Nurse, Dereham Hospital		None	
Ms Emma Murphy Independent Fetal Anti-Convulsant Trust (INFACT/FACSA)			
Ms Janet Williams Independent Fetal Anti-Convulsant Trust(INFACT/FACSA)			

Annex B

Action log for the Valproate Expert Working Group

Date	Action	Target date	By whom	Comments
29 April 2018	Explore national changes to the PIL to include reference to parents and carers	17 April 2018	MHRA	
29 April 2018	Seek legal advice on the terminology used for person taking decisions when the patient lacked capacity	16 April 2018	MHRA	
29 April 2018	Seek advice from behavioural insights experts on Risk Acknowledgement Form	5 April 2018	MHRA	
29 April 2018	Discuss with RCGP a formal shared care agreement		MHRA	Discussions ongoing
29 April 2018	Raise with NHSE whether there should be a QOF or CQUIN indicator for valproate prescribing		MHRA	Discussions ongoing
29 April 2018	Contact General Pharmaceutical Council about their role in ensuring good practice in valproate dispensing	16 April 2018	MHRA	
29 April 2018	Seek feedback from NHSI on the possibility of making an uninformed pregnancy on valproate a 'never event'	16 April 2018	MHRA	
29 April 2018	Circulate educational materials to Expert Working Group for written comments			Materials sent to members on 29th March 2018 (Risk Acknowledgement form, patient and HCP guide) and 3rd April 2018 (patient card)
29 April 2018	Members to provide comments on materials	9 April 2018	Members	
29 April 2018	Ask NHS Digital if data could be captured on the use of the search and audit tool	16 April 2018	MHRA	
29 April 2018	Follow up with the Royal College of Paediatrics and Child Health project team to assess how the Epilepsy 12 audit could	16 April 2018	MHRA	

	support the monitoring of the impact of the new measures			
29 April 2018	Consider the availability for funding and would be able to work with charities on the surveys to address resource concerns.	17 May 2018	MHRA	

Medicines & Healthcare products
Regulatory Agency

Valproate Expert Working Group

Communications to support the implementation of regulatory change

Mike Dykes (Interim Head of Patient, Public and Stakeholder Engagement)

Communications Plan

The **purpose** of the communications plan is to support implementation of the new regulatory measures

Its **objective** is to bring about changes in prescribing behaviour, such that:

- Every woman of childbearing potential currently on valproate has been reviewed by a specialist and is aware of the risks and need to take contraception
- Valproate prescribing is in the context of a Pregnancy Prevention Plan
- The number of exposed pregnancies is reduced to an absolute minimum

Communications Plan

The communications will achieve their objective by:

Making **healthcare professionals aware** of the changes to the regulatory position and their **responsibilities** to ensure that women of childbearing potential are enrolled in the Pregnancy Prevention Plan and are fully aware of the risks to the unborn child

Raising **awareness among patients** about the new regulatory measures and the impact they will have on their treatment, to facilitate women being prescribed valproate accessing the Pregnancy Prevention Plan and an annual specialist review

Overall timetable

Phasing of communications 2018/19

1. **EU Announcement:** March 23
2. **MHRA Communications:** April 17th (tbc)
3. **VSN communications :** April 17 – May 31
4. **Support**: June 1 – February 15
5. **Evaluation**: March 2019

What we have announced

March 23rd: Responsive statement welcoming the EMA announcement and update MHRA Gov.uk web page to be clear on the new regulatory position

- Valproate should be **contraindicated** in pregnancy and women of childbearing potential not using effective contraception.
- Contraindication should be supported by a **'Pregnancy Prevention Programme'**
- A **signed 'acknowledgement of risk form** should be routinely used when women are reviewed on an annual basis by a specialist.
- A **pictogram**

What we plan to announce

w/c April 16th: Communication of the *new* requirements, education materials *and* other measures being taken across the system to support and embed the changes in prescribing practice

- Letter to HCPs on actions to take
- Communications from Royal Colleges and the Royal Pharmaceutical Society
- NICE guidance mentioning valproate updated to reflect new regulatory position
- System changes including new GP alerts facilitated by NHS Digital
- Updated information materials including Patient Information Leaflet
- New education materials for healthcare professionals and patients
- Warning stickers for packs bearing the "pictogram" pending availability of new packs

Overall approach – what is different from 2016?

Mandatory changes – Pregnancy Prevention Programme

Medical cascade - briefing medical journals (e.g. PJ, Lancet, Pulse) to request they carry our messages and with support of the Royal Colleges/HCP representative bodies at senior level

Public health partners – NHSI, NHS Digital, NICE (working to have a consistent message issued at the same time)

Information at point of care – NHS Digital changes to GP software systems

Overall approach – strategic channels

Leverage of healthcare professionals' leadership

- A system response (joint announcements/public health partners)
- Engagement of the highest level clinical leadership (leaders of Royal Colleges/professional associations)

Utilise combined reach of Valproate Stakeholders' Network

- Provide central messaging
- VSN reach can communicate to 180,000+ HCPs and empower patients to challenge those responsible for their care (360,000+ main channels) and direct to thousands of GP surgeries; CCGs; Trusts and Foundation Trusts
- Patient led initiatives such as a 'Valproate Day'

Ensure the patient voice is a prominent part of communications to convey real life impact to professionals

Evaluation

- Available routes for tracking performance indicators related to communication process:
  - CQC DSU compliance data
  - Hardcopy distribution figures

- Range of studies using national data to monitor prescribing trends in women, use in and around pregnancy, and adherence to the use of effective contraception.

- Host up-to-date links to these data on our Gov.uk webpage.

Thank you and any questions?

Key Messages

UK Europe taking new regulatory action to avoid valproate use in pregnancy:

- Valproate is now contraindicated in pregnancy and in women of childbearing potential who do not comply with the Pregnancy Prevention Programme
- Female patients on valproate of childbearing potential, should be enrolled in a Pregnancy Prevention Plan
- Implementation of changes will be over a period of time: new patients should be started on a Pregnancy Prevention Plan, existing patients will be reviewed over the coming months
- GPs should identify female patients of childbearing age and ensure they understand risks, are on effective contraception and have annual review
- Specialist prescribers to ensure all patients have their treatment reviewed and treatment continued only under the Pregnancy Prevention Plan

Key Messages

Pharmacists, GPs, neurologists and other relevant healthcare professionals are expected to understand new restrictions and prescribe valproate to women of child bearing potential only within the Pregnancy Prevention Plan

New regulatory measures are being **supported across NHS** with other bodies making changes – such as new GP system alerts - to facilitate changes in prescribing behaviour

Patients & Public No woman should stop taking valproate without first discussing it with a relevant healthcare professional

Valproate is an important medicine for some women, although the serious risks to babies born to women taking the drug are well known - we are taking action to avoid further harm from valproate use in pregnancy

We are asking all women on valproate to understand need for and comply with Pregnancy Prevention Plan and to have annual review with their specialist healthcare professional

Annex D

Valproate Stakeholders' Network

List of actions committed to support implementation of the new measures March 2018

Stakeholder	Dates
Association of British Neurologists – Editorial in *Practical Neurology* Podcast by Sanjay Sisodiya Advisory papers on website	March March March
British National Formulary – *British National Formulary/C* content update	April (digital) September (print)
Epilepsy Action – Promote through social media, website, newsletters and helpline Help with producing a layperson's guide APPG on Epilepsy (Secretariat)	March onwards
Epilepsy Research UK – Promote through newsletters Collaborate to produce a layperson's leaflet	March onwards
FACSaware – Article in NHS Clinical Commissioners bulletin Blog for Epilepsy Society Promote through weekly stall at Leicester Centre for Integrated Living and YouTube channel	February February March onwards

INFACT/FACSA – Promote through website and social media APPG on Valproate (Secretariat) Conference in London	March onwards June
MIND – Promote through website, social media, helpline and online peer support community	March onwards
NHS Digital – Changes to GP software systems to facilitate audit of patients and implement a targeted warning flag	March
NHS England – Disseminate messages through professional bodies and Regional Medicines Optimisation Committees	April onwards
NHS Improvement – Use the MSO network to further support getting appropriate messages to frontline staff (monthly webinars) Work with CQC to ensure PS Alerts (incl. valproate) form a part of their inspection regimen to ensure actions embedded in practice Use the monthly *Provider Bulletin* to get messages to trust directors	March onwards
NICE – Strengthen existing warnings around the use of sodium valproate in relevant clinical guidelines: • *Epilepsies: diagnosis and management (CG137)* • *Bipolar disorder: assessment and management (CG185)* • *Antenatal and postnatal mental health: clinical management and service guidance (CG192)* Amend *Quality standard QS115 (Antenatal and postnatal mental health)* Promote through social media and NICE publications (issued daily, weekly and monthly)	April onwards
Royal College of General Practitioners –	

Raise awareness with members and encourage practices to audit their patient records to identify patients at risk Refine existing educational materials for members about this issue. National Conference (Glasgow)	April onwards October
Royal College of Midwives – Communication with membership using social media Update for the RCM epilepsy i-module with the recommendations as soon as they have been agreed News report for the RCM magazine Education conference Activists conference Annual conference	 April onwards June July October
Royal College of Paediatrics and Child Health – *President's Newsletter* (quarterly, for members) Spring RCPCH Conference Update the medicines for children website https://www.medicinesforchildren.org.uk Newsletter to all paediatricians highlighting position when final Opinion piece in Archives of Disease in Childhood Update of all standardised paediatric epilepsy courses (PET- see www.bpna.org)	 March onwards
Royal College of Psychiatrists – Article in the *British Medical Journal* Nationalisation of the GMMH *Prescribing Protocol* Form an expert group to address discussing the clinical implications and develop clinical expert guidance to prescribers for complex cases	 TBC March April onwards
Royal Pharmaceutical Society – Articles in the *Pharmaceutical Journal*	 April onwards

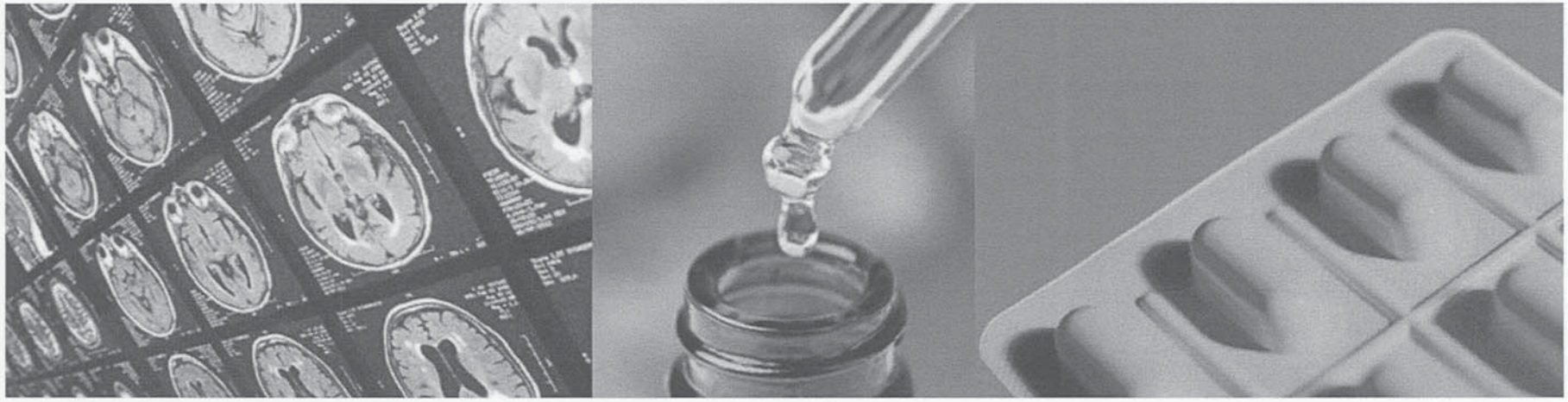
Revised *Medicines, Ethics and Practice guide* (annual publication for members) Revised website resource and *quick reference guide* Work with RCGP and MHRA to revise the youtube video for HCPs Raise the topic with pharmacy leaders and at local engagement meetings with pharmacists Email alerts to members Annual RPS medicines safety conference in Cardiff	 September
UK Teratology Information Service (UKTIS) - HCP Monographs & *bumps* patient information leaflets updated to highlight updated guidance Use of existing social media channels and links with international organisations to raise awareness Include in teaching materials: Joint ENTIS/OTIS Conference and Teratology Education Course (Newcastle upon Tyne, UK, 4-8 Sept 2018) http://www.uktis.org/html/education-course-registration.html Report on data collected through UKTIS relating to valproate exposure in pregnancy to the MHRA.	March onwards September

Medicines & Healthcare products
Regulatory Agency

Annex E

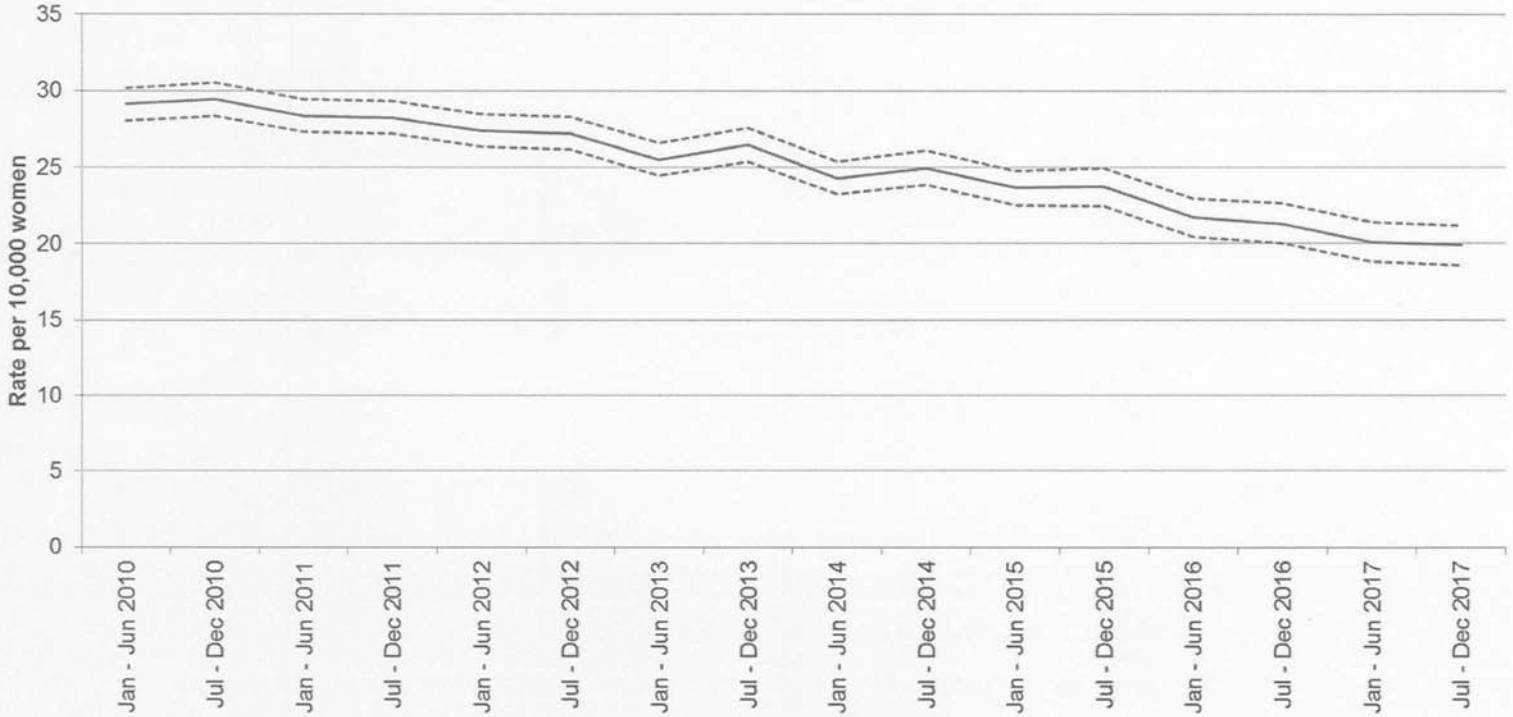
MHRA
Regulating Medicines and Medical Devices

Monitoring the impact of new risk minimisation measures

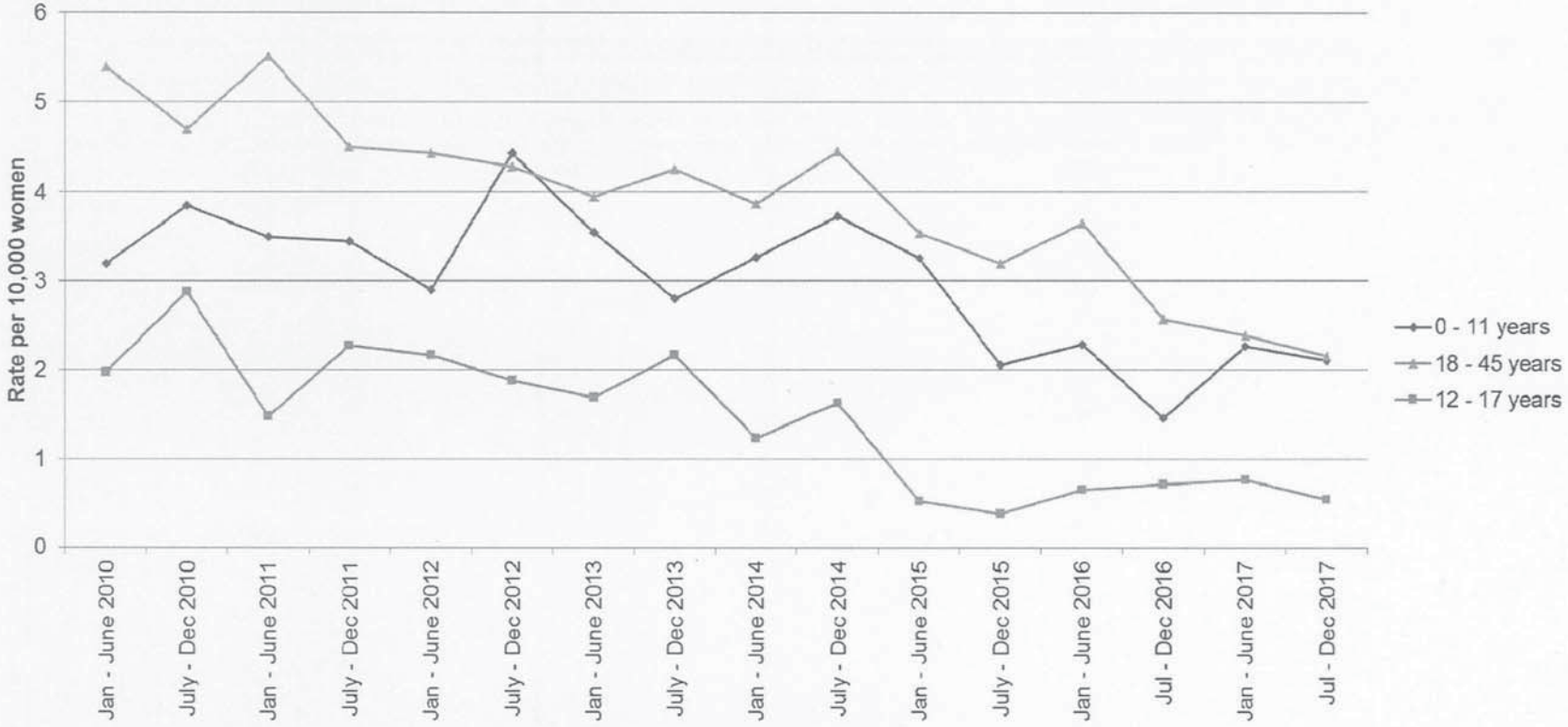


Most recent CPRD data…

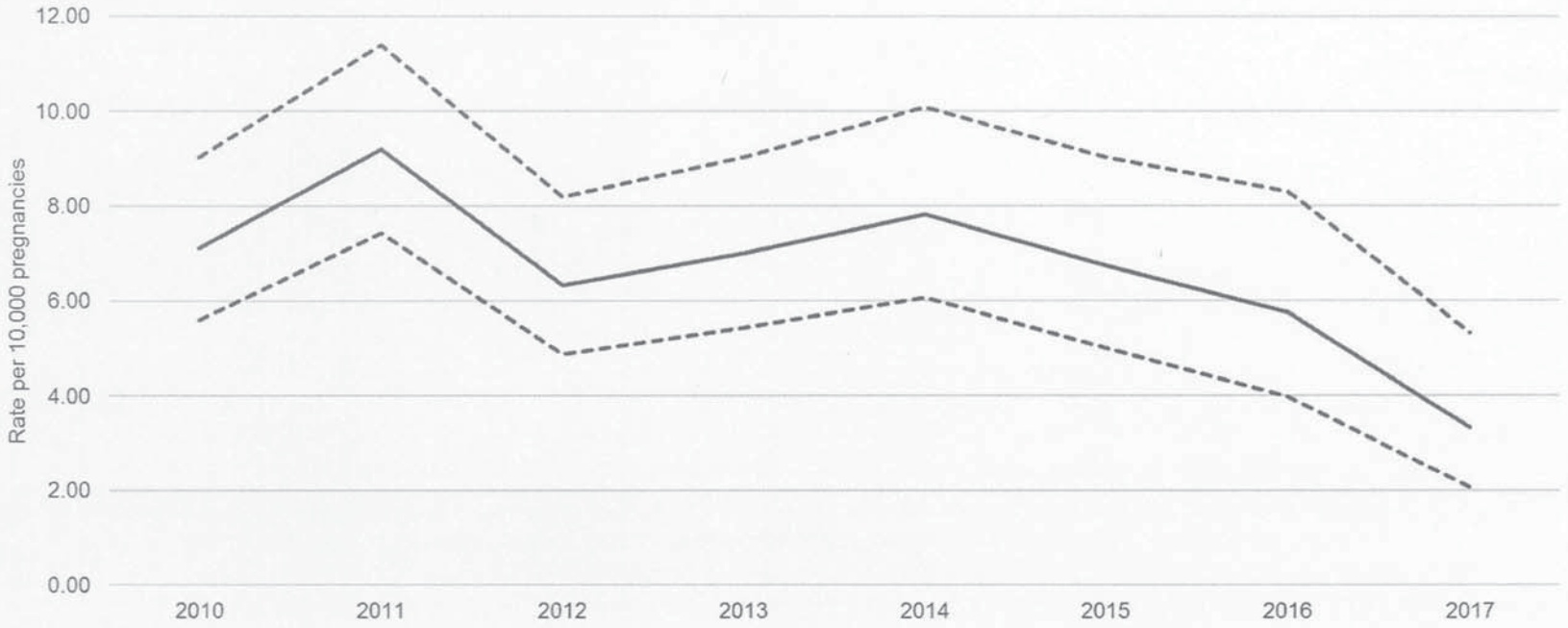
Rate of prescriptions of VPA 2010-17



Rates of new prescriptions of VPA by age 2010-17



Valproate prescribing in pregnancy 2010-17



How should we measure effectiveness?

- Necessary in order to establish if we are having the desired effect, and if not why not and what corrective actions are needed
  - Conducted at an appropriate time and tracked going forward
  - Address process, impact on knowledge, and behavioral change
  - Need to consider each element of the risk minimisation as well as the plan as a whole
  - Consideration given to what can be realistically and reliably measured

- Awareness of risks and risk minimization & process indicators
- Use of PPP i.e. use of effective contraception, acknowledgement of risk form
- Prescribing rates in women and specifically in pregnancy

Prescribing rates & practices

MHRA will continue CPRD analysis (6-monthly)

- New and repeat prescriptions
- Prescribing in different age groups
- Use in and around pregnancy
- Rates of new referral to secondary care and switching (feasibility assessment needed)

National data also required:

- NHS BSA providing English CCG level data on new and repeat prescribing https://www.nhsbsa.nhs.uk/prescription-data/prescribing-data/sodium-valproate (updated quarterly)
- Linking prescribing of contraceptives and NHS Digital linking HES maternity data – use in pregnancy (feasibility being assessed)
- Similar analyses being explored in Scotland
- Once agreed, feasibility of roll out to N Ireland/Wales will be assessed

MAH studies and UK registry

Following conclusion of the referral the MAHs are required to conduct studies to evaluate the effectiveness of the RMMs.

- "Extended Joint DUS to assess the effectiveness of the updated risk minimisation measures including PPP and to further characterise the prescribing patterns for valproate"
- "Survey among HCP to assess knowledge of HCP and behaviour with regard to PPP as well as receipt/use of DHPC and educational materials."

UK registry

- Extended to a wider registry to capture data on as many exposed pregnancies as possible across the UK
- Should facilitate exploration of adherence to PPP

Patient awareness surveys

Charity organisations have previously conducted surveys of patient awareness of the risks associated with sodium valproate when used in pregnancy

- Options for repeating with same groups through the Valproate Stakeholders Network and extending
- Additional HCP surveys could be considered at a later date

MAH patient survey also required:

- "Survey among patients to assess knowledge of the patients with regards to PPP as well as receipt/use of educational materials."

Discussion

MHRA commit to updating EWG with new data

- Will also publish (or link to as appropriate) on gov.uk page
- Via network will communicate data more widely to support local action

<u>For discussion:</u>

Are there any comments on the proposals made here?

Are there any additional aspects regarding the use of valproate that we should be monitoring to assess the effectiveness of the PPP and communications?

Are there any additional data sources that could be explored?

Annex F

Implementation of the strengthened regulatory position for valproate - timetable of next steps

Date	Action
W/C 16 April	MHRA to communicate new regulatory changes – • Central Alerting System message • Article in Drug Safety Update • Updated Summary of Product Characteristics and Patient Information Leaflet available on EMC • Electronic versions of educational materials available on EMC NICE guidelines mentioning valproate to be updated Valproate alerts across GP prescribing systems to be updated
May	Sanofi to distribute hard copy educational materials – patient guide, patient card, health professional guide, risk acknowledgement form, stickers with warning and pictogram Audience by post: • ***Hospital specialists*** *(*Child & Adolescent Psychiatry, Epilepsy, Paediatrics, Foetal medicine, Obstetrics & Gynaecology, Neurology, Psychology, Adult Psychiatry) • ***Primary care specialists*** (District Nurse Manager, District Nurse, Health Visitor Manager, Health Visitor, Midwifery Manager, Midwife Hospital, Midwife Community) • ***GPs*** • ***Community care specialists*** (Practice & Community Nurse - Adult Psychiatry, Child & Adolescent Psychiatry) • ***Hospital Nurse, Practice & Community Nurse, Tertiary Care Nurse*** *(*Child & Adolescent Psychiatry, Epilepsy, Psychology, Adult Psychiatry) • ***Medical directors*** • ***Retail pharmacists*** (Superintendent Pharmacist, Pharmacy Manager, Pharmacist Chief)

	• ***Hospital pharmacists*** (Director of Pharmaceutical Services, Medicines Management, Pharmacist Chief, Prescribing Adviser, Prescribing Lead, Pharmaceutical Adviser, Head of Medicines Management) *Delivery via Alliance tote box to 14,200 retail pharmacies*
September 18	Smaller pack size (30s) with boxed warning including pictogram in pharmacies Pictogram on blister foil
December 18	30's pack size with patient card attached to outer packaging in pharmacies

NOT FOR PUBLICATION

COMMISSION ON HUMAN MEDICINES

SODIUM VALPROATE EXPERT WORKING GROUP

Minutes of the meeting held on Thursday 17 May 2018 at 10:30am in room G1, Ground Floor, 151 Buckingham Palace Road, Victoria, London SW1W 9SZ

Members Present

Professor Sir M Pirmohamed (Chair)
Professor J Lawrence
[1] Dr J P Leach
Professor D G C Owens
Professor P Smith
Mrs M Wang

Visiting Experts

Ms J Ashton
Ms E Murphy
Ms J Williams

Professional Staff of MHRA Present

Principal Assessor

[redacted]

Supporting specific items

[redacted]

Apologies

Professor T Barnes
Professor J H Cross
Dr M Duerden
Dr J Lynch
Dr K Miller
Dr R Mann
Ms C Pelham
Dr F Rugg-Gunn
Professor C Nelson-Piercy

Secretariat

[redacted]

[1] *participated via Teleconference*

1. Introductions, apologies and announcements

1.1 The Chair welcomed to group to its 5th meeting. The Chair reminded Members, Invited Experts and Observers that the papers and proceedings were confidential and should not be disclosed.

1.2 Apologies were received from:

- Professor Thomas Barnes
- Dr Karen Miller
- Dr Fergus Rugg-Gunn
- Dr Martin Duerden
- Ms Clare Pelham
- Dr Janine Lynch
- Professor J Helen Cross
- Dr R Mann

1.3 The Chair welcomed:

- **Ms Juliet Ashton**
  Adult Epilepsy Specialist Nurse, Dereham Hospital
- **Ms Emma Murphy** and **Ms Janet Williams**
  Independent Fetal Anti-Convulsant Trust (INFACT)

who attended as an Invited Experts for the meeting.

1.4 The Chair reminded Members and Invited Experts present to declare their personal specific, personal non-specific, non-personal specific and non-personal non-specific interests in the agenda items if they had not done so prior to the meeting. Members were asked to declare interests in the associated companies Annex A of the Minutes of the meeting held on 29th March 2018.

1.4.1 All interests declared are listed at Annex A (page 6) to the minutes, members and invited experts declared no interests in the companies at the meeting.

2 Minutes of the meeting held on the 29th March 2018

2.1 The minutes were signed as a true and accurate record of the proceedings.

3. Matters arising from 29 March (action points)

3.1 The Group heard a summary of the progress and completed actions from the Action Log. It was agreed that the updated log would be circulated with the minutes and this is provided in Annex B (page 11).

3.2 The Group discussed concerns regarding the proposal for national shared care agreements. Currently these are agreed locally, and the Group discussed the potential difficulties associated with introducing such arrangements nationally and suggested that MHRA write to the Medical Director of NHSE and equivalent contacts in the devolved administrations and copy RCGP.

4. Update on implementation of new regulatory position – for information/comments

4.1 Communications from CMOs/MHRA

4.1.1 The Group was informed that the communication from Professor Dame Sally Davies (CMO England) was distributed as planned through the CAS Alert system on 24 April 2018 and that the CMO's in the devolved nations issued similar communications.

4.2 Dissemination of educational materials

4.2.1 The Group discussed the agreed educational materials. Following the recommendation from the Group at the last meeting, input had been sought from the behavioural insight group at the Department of Health. This had been very useful, and their recommendations had been incorporated into the documents.

4.2.2 The Group raised a number of points regarding the content and presentation of the Annual Acknowledgement of Risk Form and how this could be improved. The MHRA said they would try get these incorporated.

4.2.3 The Group also discussed points which could be incorporated into subsequent versions of the educational materials. In particular the Group were keen to ensure that the issue of capacity was adequately addressed in the materials and advised that the recommendations about the use of the PPP in adolescent girls needed further discussion. Other points included the use of bold in the patient guide to help clarify or highlight the differences between doctor and specialist, as patients may need to contact different healthcare professionals for different aspects of their care. The Group was asked to provide any comments in writing.

4.2.4 The Group received positive feedback regarding the use of the materials by Specialist Nurses who may be ideally placed within the clinic to discuss these issues with patients. Prof Lawrence said that she had previously provided (and would provide again) contacts at the Centre for Pharmacy Post-graduate Education who would be important in getting messages to pharmacists.

4.3 Supportive communication plan

4.3.1 The Group was presented with an overview of the communications that had been issued and the longer-term communication plans which were welcomed by the Group.

4.3.2 The feedback on the communications issued was positive and the importance of emphasising the use in bipolar disorder was recognised, given the prominence of the previous coverage for the epilepsy indication.

4.3.3 The Group discussed plans for future presentations at conferences and events on the issue and several suggestions were made for additional events for the MHRA to consider attending and promoting the messages regarding the new regulatory requirements for valproate.

4.3.4 The Group discussed the valproate video which highlights the key issue and the importance of it being accessible. The Group recommended that it should be included on the websites of the relevant healthcare organisations.

4.3.5 The Group discussed the need to continue to raise awareness of this important issue and the possibility of further communications such as a poster or leaflet in GP's surgeries. The MHRA agreed to consider the feasibility and effectiveness of further communications to raise awareness of the risks associated with the use of medicines in pregnancy.

5.1 Draft algorithm for GPs – for advice

5.1.1 The Group was presented with a draft algorithm which had been produced in collaboration with the representative from the Royal College of General Practitioners. It was confirmed that this was an initial draft and that it could be incorporated into clinical guidance once finalised.

5.1.2 The Group acknowledged that an algorithm could be useful and highlighted a number of issues for consideration. It was acknowledged that although patients are invited to attend clinics they do not always attend and that there are particularly high rates of non-attenders within the psychiatric clinics. It was recommended that the algorithm or supporting guidance should include advice regarding action to be taken when patients do not attend (e.g. phone consultation) and that it should define who was responsible for contacting the patient again. It was also recommended that the algorithm should promote enrolment into the UK Epilepsy and Pregnancy Registry should any patients become pregnant.

5.1.3 The Group raised a concern that there may be some women who did not access GP care and would be missed. It was suggested that walk in clinics or social services may have more contact with some of the vulnerable patient groups receiving valproate, particularly those that do not attend regular clinics.

5.1.4 The Group did not think an algorithm was needed within secondary care.

6 Cumberlege Review – for information/comments

6.1 The Group reflected on the proposed review as outlined in the Ministers speech. It was confirmed that the review was independent of the MHRA, though the MHRA would be contributing as required.

6.2 The Group heard that the review is in the early stages with Baroness Cumberlege

meeting relevant groups and that the terms of reference for the review have not yet been finalised.

7 Update on monitoring the impact of action - for information

7.1 The Group were presented with an update of the actions being taken to monitor the impact of action taken as well as plans for further analysis. It was confirmed that the next batch of data should be available for consideration at the final meeting planned for the Autumn.

The Group noted that proposals were awaited from Sanofi for a valproate specific drug pregnancy registry was discussed. The Group advised that care should be taken that the development of a valproate specific registry should not adversely affect recruitment to the UK Epilepsy and Pregnancy Registry. The Group asked that Dr Leach be included in discussions about proposals.

8. Any other business

8.1 As requested at a previous meeting it was agreed that copies of valproate related parliamentary questions will be presented and that details of the questions received since the March meeting would be circulated with the minutes and these are provided in Annex C (page 14).

8. Date and time of next meeting

8.1 The next meeting of the Group likely to take place in November 2018

The meeting started at 10:35am and ended at 12:32

ANNEX A

SODIUM VALPROATE EXPERT WORKING GROUP

Register of Interests Declared by Members and Invited Experts

Chair	Interests declared up to 29th March 2018 meeting	New Interests declared 17th May 2018 meeting
Professor Sir Munir Pirmohamed MB ChB (Hons) PhD FRCP FRCP (Edin) FBPhS FMedSci	I have not specifically worked on sodium valproate in relation to this issue, but some of the work that showed the effects of sodium valproate on cognitive outcomes after foetal drug exposure was undertaken by colleagues in the University of Liverpool (Baker and Bromley). Bromley has since moved onto another University while Baker has retired. However, I was not involved in any of the work. This did not debar the Chair from chairing this Working Group.	None
Members		
Professor J Helen Cross OBE MB ChB PhD FRCP FRCPCH	My department received an educational grant from Sanofi to fund a meeting January 2017. My institution has received an educational grant for a research event from Sanofi. **Note**: The Chair ruled that this did not debar Professor Cross from taking part in the proceedings. Our department has received educational grants from Sanofi and Desitin	None
Dr Martin Duerden B Med Sci, MB BS, DRCOG, Dip Ther, DPH, FRCGP	None	None
Professor Jayne Lawrence	None	None

Dr John Paul Leach	Review of Epilepsy management in pregnancy recommended actions for a range of healthcare professionals and patients – currently in epub but due publication imminently: (Epilepsy and Pregnancy: For healthy pregnancies and happy outcomes. Suggestions for service improvements from the Multispecialty UK Epilepsy Mortality Group. Seizure. 2017 Jun 1;50:67-72. doi: 10.1016/j.seizure.2017.05.004. [Epub ahead of print] Leach JP[1], Smith PE[2], Craig J[3], Bagary M[4], Cavanagh D[5], Duncan S[6], Kelso ARC[7], Marson AG[8], McCorry D[9], Nashef L[10], Nelson-Piercy C[11], Northridge R[12], Sieradzan K[13], Thangaratinam S[14], Walker M[15], Winterbottom J[16], Reuber M[17].) Also joint grant holder from HTA looking at use of valproate in newly diagnosed epilepsy – results awaited, recruitment finished. (SANAD2) **Note**: The Chair ruled that this did not debar Dr Leach from taking part in the proceedings.	None
Dr Janine Lynch BHSCT		None
Dr Rebecca Mann BMBS FRCPCH	None	None
Dr Karen Miller BSc MBBS DRCOG DCH DFFP FRCGP	None	None
Professor Catherine Nelson-Piercy MBBSMA, FRCP, FRCOG	None	None
Professor David G C Owens MD (Hons) FRCP FRCPsych	NP-NS - Proposal from EMA to collaborate with secretariat for a publication on psychiatric literature	None
Ms Clare Pelham	I am not aware of any non-personal interests but I have asked for checks to be made within Epilepsy Society. I have not personally conducted any reviews of Sodium valproate or research. I am not aware of any product-specific interests of the Epilepsy Society, but I have asked for checks to be made and this information will follow. I have commented publicly on the desirability of information about risk during pregnancy being provided more regularly and comprehensively to woman and girls of childbearing age who have been prescribed Sodium Valproate.	None

	As I said on the completed form, the information relating to the Epilepsy Society will follow as soon as we are able to compile it. It may be helpful to note that I became Chief Executive here on 14 November 2016, and, as I said on the form, I am not personally aware of any non-personal interests or product-specific interests of the Epilepsy Society. I have never expressed any strong opinions on the merits or otherwise of the drug, sodium valproate, to the best of my recollection. My comments have focused on the provision of information.	
Dr Fergus Rugg-Gunn MB BS MRCP PhD	None	None
Ms Laura Russell	None (left the Group)	None
Professor Philip Smith	I have no product-specific interests in sodium valproate and have not undertaken research specifically on sodium valproate in isolation. However, I have participated in research that has involved sodium valproate alongside other antiepileptic medications: for example, I have randomised patients to the SANAD studies, which included sodium valproate as one of several randomised medications. I have not made any public commentary specifically on the safety of sodium valproate products. However, I give many lectures on epilepsy and included in these I will have described available research data on antiepileptic medication (including valproate). Also in the last 12 months I have been a member of the MHRA Valproate Stakeholders Group and so have made statements about sodium valproate in that forum. Note: The Chair ruled that this did not debar Professor Smith from taking part in the proceedings.	None
Mrs Madeleine Wang BA (Hons)	None	None
Invited Expert		None
Professor Thomas R. E. Barnes MD FRCPsych DSc Professor of Clinical Psychiatry, Imperial College London	I have been a co-author of the following papers:	None

	James L, Paton C, Lelliott P, Barnes TRE, Taylor D. Mood stabilizers and teratogenicity-prescribing practice and awareness amongst practising psychiatrists Journal of Mental Health 2009;18:137–143. *This study attempted to evaluate the knowledge and stated practice of consultant psychiatrists with respect to the prescribing of lithium, carbamazepine and valproate for women of child-bearing age. Semi-structured interviews were conducted with 52 consultant psychiatrists. Most prescribers (79–96%, depending on the drug) used these drugs and most (81–86%) were more cautious when prescribing to women of child-bearing age. Fewer (17–28%) demonstrated good, specific awareness of the estimated teratogenic potential of the individual drugs. Reported practice was characterized by reluctance to discuss contraception with patients, failure to prescribe prophylactic folate and uncertainty about who was clinically responsible for these issues.* James L, Barnes TRE, Lelliott P, Taylor D, Paton C. Informing patients of the teratogenic potential of mood stabilizing drugs: a case note review of the practice of psychiatrists. Journal of Psychopharmacology 2007;21:815-819. *This paper reports on a review of clinical records of women of childbearing age, under the care of one specialist mental health Trust, who were prescribed lithium and/or carbamazepine and/or valproate. The findings related to documented discussion of the risks. Specifically, there was documented evidence indicating that just over 20% of these women had been informed about teratogenicity and nearly a quarter (24%) had been advised about contraception. Fourteen women (10%) had a confirmed pregnancy while taking lithium, carbamazepine or valproate; eight had a complication of pregnancy.* BALANCE investigators and collaborators, Geddes JR, Goodwin GM, Rendell J, Azorin JM, Cipriani A, Ostacher MJ, Morriss R, Alder N, Juszczak E. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. Lancet 2010;375:385-395. *I am one of 169 named collaborators on the BALANCE study, which was an open-label RCT of lithium monotherapy, valproate monotherapy, or both agents in combination for relapse prevention in bipolar I disorder. The conclusions from the findings were that for people with bipolar I disorder, for whom long-term therapy is clinically indicated, both combination therapy with lithium plus valproate and lithium monotherapy are more likely to prevent relapse than is valproate monotherapy.*	

	BALANCE could neither reliably confirm nor refute a benefit of combination therapy compared with lithium monotherapy. I am co-clinical lead for the Prescribing Observatory for Mental Health (within the Centre for Quality Improvement at the Royal College of Psychiatrists) that issued the following report of a baseline clinical audit, part of a national quality improvement programme: Prescribing Observatory for Mental Health (2016). Topic 15a baseline audit report. Prescribing valproate for bipolar disorder. Prescribing Observatory for Mental Health, CCQI222 (data on file). In response to your query, I would not consider that the publications I mentioned in my personal interest declaration contain strong opinions for or against sodium valproate or the pharmaceutical companies. I have provided a brief summary of the papers, which may be helpful. Note: The Chair ruled that this did not debar Professor Barnes to take part in the proceedings as an invited expert.	
Visiting Experts		
Ms Juliet Ashton Adult Epilepsy Specialist Nurse, Dereham Hospital	None	None
Ms Emma Murphy **Independent Fetal Anti-Convulsant Trust (INFACT/FACSA)**	None	None
Ms Janet Williams **Independent Fetal Anti-Convulsant Trust(INFACT/FACSA)**	None	None

Annex B

Action log for the Valproate Expert Working Group

Date	Action	Target date	By whom	Comments as of 17 May 2018
29 April 2018	Explore national changes to the PIL to include reference to parents and carers	17 April 2018	MHRA	Done – PIL to include reference to parents and carers.
29 April 2018	Seek legal advice on the terminology used for person taking decisions when the patient lacked capacity	16 April 2018	MHRA	Legal advice is that 'responsible person' is the appropriate term.
29 April 2018	Seek advice from behavioural insights experts on Risk Acknowledgement Form	5 April 2018	MHRA	Done
29 April 2018	Discuss with RCGP a formal shared care agreement		MHRA	Discussions ongoing
29 April 2018	Raise with NHSE whether there should be a QOF or CQUIN indicator for valproate prescribing		MHRA	Discussions ongoing
29 April 2018	Contact General Pharmaceutical Council about their role in ensuring good practice in valproate dispensing	16 April 2018	MHRA	Done – offer to communicate in their bulletin Regulate +
29 April 2018	Seek feedback from NHSI on the possibility of making an uninformed pregnancy on valproate a 'never event'	16 April 2018	MHRA	Under consideration by NHSI
29 April 2018	Circulate educational materials to Expert Working Group for written comments			Materials sent to members on 29 March 2018 (Risk Acknowledgement form, patient and HCP guide) and 3 April 2018 (patient card)
29 April 2018	Members to provide comments on materials	9 April 2018	Members	Done
29 April 2018	Ask NHS Digital if data could be captured on the use of the search and audit tool	16 April 2018	MHRA	Feedback from NHSD awaited.

29 April 2018	Follow up with the Royal College of Paediatrics and Child Health project team to assess how the Epilepsy 12 audit could support the monitoring of the impact of the new measures	16 April 2018	MHRA	Done
29 April 2018	Consider the availability for funding and would be able to work with charities on the surveys to address resource concerns.	17 May 2018	MHRA	To consider during planning of surveys
Actions as of 17 May 2018				
17 May 2018	Write to Medical Director NHSE and relevant contacts in Devolved administrations to as for shared care agreement for valproate	June 2018	MHRA	Post meeting note – there was subsequent discussion of shared care agreements at the ministerial meeting with clinical leads on 19th June. Proposals for action will be sent to the minister.
17 May 2017	Incorporate final changes to Annual Acknowledgment of Risk form	19 May 2018	MHRA	Done
17 May 2018	Members to provide any comments on the patient and HCP brochure in writing to MHRA		Members	Done
17 May 2017	Prof Lawrence to provide details of CPPE contacts	17 May 2018	Prof Lawrence	Done
17 May 2018	Update draft algorithm to include advice on action to take if patients do not attend appointments and a request to include any exposed pregnancies into the antiepileptics pregnancy registry.	25 May 2018	MHRA	
17 May 2018	Consider reaching out to contact points for vulnerable patient groups – walk in centres or social services.		MHRA	Ongoing
17 May 2018	Attach record of Parliamentary questions relating to valproate to minutes of the meeting	31 May 2018	MHRA	

17 May 2018	Involve Dr Leach in discussions on valproate registry		MHRA	Ongoing
18 May 2018	Comms around release of materials. Confirmed email to VSN with link to copies of the finalised materials. Will also ask key stakeholders incl. RCGP, RPS and ABN to link to the GOV.UK page from their websites. Ditto social media. Separate email to CPPE who can send info to pharmacists and technicians.	18 May 2018	MHRA	Done
	New valproate video – make sure it's on relevant royal college and other websites	Autumn 2018	MHRA	
	Posters. Agreed but concern they get covered up. INFACT suggested a simple leaflet as well explaining issues. Comms to consider this.	Autumn 2018	MHRA	
	Strapline: Suggested 'No pregnancy for uniformed women'. Comms to think about this and use in future comms.	Autumn 2018	MHRA	
	Events. Several suggestions made. Royal College of Psychiatrists in June. Epilepsy Specialist Nurses Association (ESNA) conference Manchester 19-20 June. EWG to recommend other conferences to Paul Inglefield.	From June 2018	MHRA	

Annex C

Parliamentary questions and responses on valproate Jan-May 2018

The Rt Hon Norman Lamb MP (North Norfolk) (Liberal Democrats) To ask the Secretary of State for Health and Social Care, what resources he plans to commit his Department and its agencies to provide to improve patient safety and engage with health professionals to raise awareness of the potential health risks for women of child-bearing age taking Sodium Valproate; and if he will make a statement. PQ136233

Reply

The Medicines and Healthcare products Regulatory Agency (MHRA) has been working in partnership with the Department for Health and Social Care, professional bodies and the healthcare system to bring together a package of measures to raise awareness of the significant risks associated with sodium valproate in pregnancy and to support healthcare professionals in reducing the harms from valproate in women of child-bearing age. All parties involved are fully committed to this important work using the existing resources each relevant organisation.

The new measures include updated educational materials for healthcare professionals and patients and will be communicated through the MHRA bulletin and letters to healthcare professionals through the NHS Central Alerting System. The information cascade will be supported by messages from professional bodies, charities and patient groups to their constituents and reinforced through changes to clinical guidelines and improved alerts on GP prescribing systems.

The effectiveness of the new measures in changing prescribing of valproate will be closely monitored. Relevant data will be published and there will be ongoing follow up to ensure that the harms to the child from valproate in pregnancy are minimised.

James Frith MP (Bury North) (Labour) To ask the Secretary of State for Health and Social Care, what estimate his Department has made of funding required to raise awareness of the potential health risks for women of child-bearing age of taking Sodium Valproate. PQ136717

Reply

The Medicines and Healthcare products Regulatory Agency (MHRA) has been working in partnership with the Department for Health and Social Care, professional bodies and the healthcare system to bring together a package of measures to raise awareness of the significant risks associated with sodium valproate in pregnancy and to support healthcare professionals in changing prescribing behaviour and therefore reducing the harms from valproate in women of child-bearing age. All parties involved are fully committed to the implementation of the new regulatory position using the existing funds of each relevant organisation.

The new measures include updated educational materials for healthcare professionals and patients and will be communicated through the MHRA bulletin and letters to healthcare professionals through the National Health Service Central Alerting System. The information cascade will be supported by messages from professional bodies, charities and patient groups to their constituents and reinforced through changes to clinical guidelines and improved alerts on General Practitioner prescribing systems.
The effectiveness of the new measures in changing prescribing of valproate will be closely monitored. Relevant data will be published and there will be ongoing follow up to ensure that the harms to the child from valproate in pregnancy are minimised.

Kate Osamor MP (Edmonton) (Labour) To ask the Secretary of State for Health and Social Care, if he will take steps to (a) investigate the lack of information given to pregnant women prescribed with sodium valproate in the 1970s and (b) introduce a national compensation fund for people affected by the effects of sodium valproate being prescribed to pregnant women. PQ131076
Reply
Sodium valproate was marketed for general use in epilepsy in 1974. The first datasheet (information which was provided to healthcare professionals about how to use the medicine) included a warning about the possible risk of birth defects (teratogenicity) which was based on animal studies. The warning stated that “In women of childbearing age, the product should only be used in severe cases or in those resistant to other treatment.” and “Precautions – women of childbearing age: this compound has been shown to be teratogenic in animals. Any benefit which may be expected from its use should be weighed against the hazard suggested by these findings.” Over the years, as new data have become available on the risks associated with valproate in pregnancy the warnings in the information provided with the medicine have been updated.
Since 1999, legislation has ensured that medicines are accompanied by a Patient Information leaflet which includes information on all the known risks associated with the medicine. Prior to that it was left to the judgement of the doctor to decide how much information should be shared with a patient about their medical care.
The Government has great sympathy for those families who have been affected by the use of valproate in pregnancy. However, there is currently no proposal to offer compensation for those affected by the use of valproate during pregnancy in the UK. For any child born with a disability, clinical commissioning groups and local authorities, as commissioners of health and social care must secure services to meet the child’s needs. Where a child has a very complex health need, they may need additional health support to that which is routinely available from GP practices, hospitals or in the community, called continuing care. Health, social care and education should work together to meet the needs of children and young people with special educational needs.

Cat Smith MP (Lancaster and Fleetwood) (Labour) To ask the Secretary of State for Health and Social Care, which NHS prescription drugs contain (a) Valproate and (b) Sodium Valproate or their derivatives; and what warnings are given to patients of the associated risks to pregnant women. PQ131406

Reply

The name valproate is often used to describe several medicines used in the treatment of epilepsy and bipolar disorder – sodium valproate, semisodium valproate and valproic acid.

Sodium valproate is the active constituent of the following brands of prescription drugs authorised in the UK: Epilim, Episenta, Sodium valproate Zentiva, Convulex, Sodium valproate Ivax, Valprotek, Epival, Orlept, and Sodium valproate Teva.

Valproate semisodium is the constituent of Depakote tablets and Syonell gastro resistant tablets.

All formulations of valproate (sodium valproate, valproic acid and valproate semisodium) carry a risk of birth defects if taken by pregnant women and should only be used to treat women of childbearing potential and girls if other drugs are ineffective or not tolerated. Over the years the evidence of risk has grown and following a European review on the risks of developmental disorders, which completed in 2014, there has been extensive work to communicate clear advice to health professionals and patients. Warnings about the risks of valproate if taken during pregnancy and that females of childbearing age should use an effective method of contraception throughout treatment are included in a boxed warning in the package leaflet which accompanies the medicine. This leaflet also provides detailed information of the magnitude and nature of the risk, details of the actions patients need to take, where to find addition information and the importance of discussing this with their doctor.

Warnings are present on the outer packaging of the medicine and in a patient card which should be provided by the pharmacist when valproate is dispensed. Further information on the risks is provided in a patient guide to be used to support discussions between the woman and her doctor.

A further European review, initiated because of concerns about the effectiveness of measures taken to date, will complete shortly. It will deliver a strengthened regulatory position which will enable a more structured and systematic approach, through a pregnancy prevention programme, to ensure that women understand and accept the risks of treatment, are supported in making informed choices about contraception and that there is specialist supervision and monitoring if they chose to continue with valproate treatment.

Product Licence of Rights for Hormone Pregnancy Tests:

The PLRs for the following can be found in the supporting documents to the Report of the Commision on Human Medicines' Expert Working Group on Hormone Pregnancy Tests:

- Paralut Forte Injection
- Paralut Forte Tablets
- Paralut Injection
- Paralut Tablets

https://mhra.filecamp.com/public/files/2r9f-3n0iiqf5

Additional PLRS are attached.

PRODUCT LICENCE OF RIGHT No.

APPLICATION FOR PRODUCT LICENCES OF RIGHT

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February, 1972

Schering Chemicals Limited
Burgess Hill
Sussex

PRODUCT LICENCE OF RIGHT No. 0063/5027

[redacted]

APPLICATION FOR LICENCE OF RIGHT

TO MARKET

PRIMODOS COATED TABLETS 10 mg.

==========

Schering Chemicals Limited
Burgess Hill
Sussex

PRODUCT LICENCE OF RIGHT No. 0053/5027

1. NAME AND ADDRESS OF THE APPLICANT

[redacted]

Schering Chemicals Limited
Burgess Hill
Sussex

2. NAME AND ADDRESS OF THE PROPOSED LICENSEE

Schering Chemicals Limited
Burgess Hill
Sussex

3. ROLE OF PROPOSED LICENSEE

The proposed licensee imports the product from Germany for sale in the United Kingdom.

4. NAME AND ADDRESS OF THE ACTUAL IMPORTER

As for 2

5. PERIOD OF VALIDITY OF THE LICENCE

Five years

6. ACTIVITIES COVERED BY THE LICENCE

The licence will authorise the importation of the product and its sale and supply in the United Kingdom.

PRODUCT LICENCE OF RIGHT No. 0053/5027

[redacted]

7. Name of Medicinal Product:

Primodos

8. Pharmaceutical Form:

Tablet for oral administration to human beings

9. Composition:

(a) Active ingredients

1 coated tablet contains:

10.0	mg.	Norethisterone acetate
0.02	mg.	17α-ethinyl oestradiol

(b) Other ingredients

1 coated tablet contains:

1.00	mg.	Magnesium stearate
44.98	mg.	Starch
69.00	mg.	Lactose
50.615	mg.	Sugar
29.628	mg.	Talc
2.999	mg.	Calcium carbonate, precipitated
0.56	mg.	Polyvinylpyrrolidone K90 (Luviskol K90)
0.078	mg.	Gelatin
0.005	mg.	Sodium benzoate
0.08	mg.	White wax
0.04	mg.	Carnauba wax
0.995	mg.	Tartrazine, food colour yellow No. 2.

[redacted]

10. Physical Characteristics:

Orange-yellow, lustrous coated tablets of about 7.8 mm diameter and about 4.3 mm height

11. Clinical Use:

(a) Recommended clinical use

Secondary Amenorrhoea

(b) Route of Administration

Oral

(c) Recommended dosage

Adults

1 tablet on each of two consecutive days.
Bleeding usually follows in 3 - 6 days.

Children

Not for administration to children

12. Standard Provisions:

No comment

SCHERING AG

PRODUCT LICENCE OF RIGHT No. 0053/5027

Pharma Koordination

23.2.1971

[redacted]

13. Manufacture and Assembly

(a) Summary of manufacturing procedure

Abridged Manufacturing Formula

P r i m o d o s

1. Granulation

1.1 Starch paste

1.1.1 A portion of the starch is stirred into the demineralized water.

1.1.2 Levigation (1.1.1) is added to boiling, demineralized water and heated till it forms a paste.

1.2 Manufacturing of granulation

1.2.1 Ethinyl estradiol is dissolved in alcohol.

1.2.2 Solution (1.2.1) is mixed with some of the starch.

1.2.3 Mixture (1.2.2) is dried.

1.2.4 Norethisterone acetate micro 2 is mixed with some of the lactose.

1.2.5 Mixture (1.2.3) is screened and mixed with preparation (1.2.4), with lactose and with a portion of the starch.

1.2.6 The powder mixture (1.2.5) is kneaded with the starch paste (1.1).

1.2.7 The moist mass (1.2.6) is granulated and dried.

1.2.8 The dried granules are made uniform.

1.2.9 The uniform granules (1.2.8) are mixed with magnesium stearate and the remainder of the starch.

2. Cores

The granulation is pressed to form cores.

3. Coated tablets

3.1 Preparations for applying the tablet coating.

SCHERING AG

[redacted]

13. (a) 3.1.1 Suspension

3.1.1.1 Polyvinylpyrrolidone K 90 is dissolved in benzene-denatured alcohol.

3.1.1.2 A portion of the talc is suspended in the solution (3.1.1.1)

3.1.2 Solution I

3.1.2.1 Gelatin and sodium benzoate are dissolved in demineralized water.

3.1.2.2 A portion of the sucrose is dissolved in demineralized water.

3.1.2.3 Solutions (3.1.2.1) and (3.1.2.2) are mixed.

3.1.3 Solution 2

Identical to solution (3.1.2.2)

3.1.4 Color solution I

A portion of the food-color yellow No. 2 and a portion of the sucrose are dissolved in demineralized water.

3.1.5 Color solution 2

The remainder of the food-color yellow No. 2 and the remainder of the sucrose are dissolved in demineralized water.

3.1.6 Powder

The precipitated calcium carbonate is mixed with the talc.

3.1.7 Wax mixture.

3.1.7.1 White wax and carnauba wax are melted together.

3.1.7.2 The inside of the pan is coated with the melt (3.1.7.1).

SCHERING AG

13 (a) 3.2 Coating [redacted]

3.2.1 Suspension (3.1.1) is applied to the cores.

3.2.2 Solution I (3.1.2) and the powder (3.1.6) are applied.

3.2.3 Solution 2 (3.1.3) is applied.

3.2.4 Color solution I (3.1.4) is applied.

3.2.5 Color solution 2 (3.1.5) is applied.

3.3 Polishing

The coated tablets are polished in the wax pan (3.1.7.2). They are finally dried.

Jo/Lü

(signed by Dr. [redacted])

PRODUCT LICENCE OF RIGHT No. 0053/5027

13. (b) Manufacture and assembly of this preparation take place at the production plants of Schering AG., Berlin/Bergkamen at the following addresses: [redacted]

1 Berlin 65
Müllerstrasse 170-172
Germany

(c) Manufacturer

Schering AG., Berlin/Bergkamen,
Berlin 65
Mullerstrasse 170-172
Germany

(d) Storage

Pending Customs clearance at Shoreham Port the imported products are stored at the following address:

P.D. Wharfage Co. Ltd.,
Aldrington Basin
Shoreham, Sussex

After a period of temporary storage the goods are transferred to one of the following addresses:

Schering Chemicals Limited
(Warehouse)
Victoria Way
Burgess Hill
Sussex

or

(Warehouse)
London Road
Burgess Hill
Sussex

Conditions of even temperature and humidity exist in all premises and comply with the manufacturers' specifications for storage of the product.

14. Quality control over method of pharmaceutical manufacture:

(a) Tablet and coated tablet preparations [redacted]

Control measures during manufacture

1. Active and inactive substances are employed for manufacturing processes in the production unit only after being released by the analytical control laboratory.

2. Granulations are prepared according to a batch production sheet which has been prepared by the unit director or a person whom he has designated. The initial weights of active and inactive substances are always determined by two persons, the unit director and/or persons designated by him. Both persons must sign the batch production sheet.

3. A sample of the finished granulation is sent to the analytical control laboratory for testing according to the testing standard currently in effect.

4. Following release, the granulation is compressed to form tablets or tablet cores. In the course of this process, the weight, height, hardness and disintegration speed of the unfinished pressings are tested at regular intervals and the results entered on the work record sheets.

5. Samples of the finished tablets or cores are turned over to the analytical control laboratory for testing according to the appropriate testing standard.

6. Following release by the analytical control laboratory, the cores are weighed on a regular basis during the coating process in accordance with the specifications contained in the manufacturing formulas.

7. The coated tablets are tested in the analytical control laboratory according to the testing standard 2 D 01 07 c.

8. After the lots of tablets and coated tablets have been released, the unit director or his authorized representative checks identity (form, size, color, weight) against the specifications on the lot cards before packaging begins.

9. Reserve specimens from each lot are retained for some years both in the analytical control laboratory and at the manufacturing unit.

PRODUCT LICENCE OF RIGHT No. 0053/5027

[redacted]

14. (b) Our Parent Company, Schering AG., Berlin/Bergkamen, as manufacturer of the product, is responsible for deciding whether any batch is of acceptable quality for marketing

15. Containers:

Primodos is supplied in a two-tablet foil pack

16. Labelling:

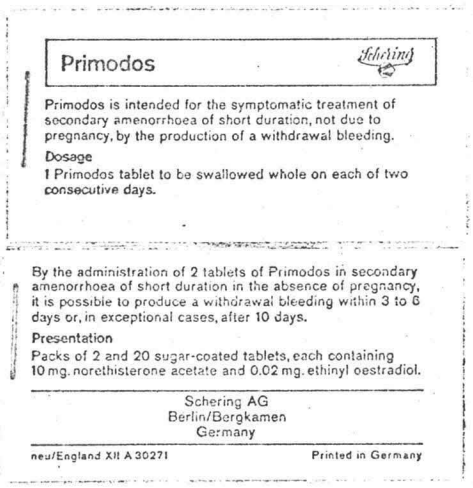
(a) Container

Oral

(b) Package

No special directions

(c) Package Leaflet



Primodos

Schering

Primodos is intended for the symptomatic treatment of secondary amenorrhoea of short duration, not due to pregnancy, by the production of a withdrawal bleeding.

Dosage

1 Primodos tablet to be swallowed whole on each of two consecutive days.

By the administration of 2 tablets of Primodos in secondary amenorrhoea of short duration in the absence of pregnancy, it is possible to produce a withdrawal bleeding within 3 to 6 days or, in exceptional cases, after 10 days.

Presentation

Packs of 2 and 20 sugar-coated tablets, each containing 10 mg. norethisterone acetate and 0.02 mg. ethinyl oestradiol.

Schering AG
Berlin/Bergkamen
Germany

neu/England XII A 30271 Printed in Germany

PRODUCT LICENCE OF RIGHT No.

0053/5027

[redacted]

17. Method of Sale and Supply:

(a) This preparation was made available, on prescription only, prior to 1964.

(b) Entry from MIMS Monthly Index, August, 1971.

PRIMODOS Schering
*Norethisterone acetate 10 mg., ethinyloestradiol 0·02 mg.; tab.**
Amenorrhoea not due to pregnancy.
2, 29p.; also 20.
1 on two consecutive days.

(c) No changes in the method of sale and supply of this product are proposed

18. Therapeutic Substances Act and Diseases of Animals Act:

Not applicable

Licence Nos. 0053/5019 TO 5038

MEDICINES ACTS 1968 AND 1971

A **PRODUCT LICENCE OF RIGHT** has been granted under and subject to the provisions of the Medicines Acts 1968 and 1971 to

SCHERING CHEMICALS LIMITED,
BURGESS HILL,
SUSSEX.

to authorise the dealings described in Part 1 of the attached Schedule in the products and under the licence numbers therein specified. The licence is subject to the further provisions set out or referred to in Part 2 of the said Schedule.

The licence, unless previously suspended, revoked or varied as to the period of its validity, shall continue in force until the end of a period of five years from the date on which it was granted.

Date granted : 10 NOVEMBER 1972. [redacted]

A person authorised to
sign on behalf of the
Secretary of State for
Social Services.

10 NOVEMBER 1972.

Department of Health and Social Security,
Finsbury Square House,
33/37A, Finsbury Square,
London, E.C.2.

NOTICE

The existence of a product licence of right in respect of a particular product does not imply that the safety, quality or efficacy of the product has been considered by the licensing authority.

Under section 25 of the Medicines Act 1968 the licensing authority is required to grant such a licence to any applicant who proves that he fulfils certain conditions as to his dealings in the product before 1 September 1971. The licensing authority has power, normally after consulting the appropriate committee, to suspend, revoke or vary such a licence on specified grounds, which include considerations of safety, quality or efficacy.

After a date to be fixed by statutory order under Section 52 of the Medicines Act 1968, it will not be lawful (notwithstanding any provision in the relevant licence of right) to sell by retail any medicinal product otherwise than from a registered pharmacy unless the product is included on a general sale list or is covered by one of the statutory exemptions under sections 55 or 56 of the Act or by any exemption made by order under section 57 of the Act.

MEDICINES ACTS 1968 AND 1971

Product Licence of Right No. 0053/5019 TO 5038

Part 1 - PARTICULARS OF THE DEALINGS, PRODUCTS AND LICENCE NUMBERS

1. The licence authorises the holder of the licence to import and to sell or supply the medicinal products, or to procure the sale or supply of the medicinal products so imported, being the products described in the holder's application dated 8 FEBRUARY 1972 and denoted on the attached copy of the said application by the respective licence numbers 0053/5019 TO 5038 under the product names set out therein.

2. The number so denoted shall be the licence number of the product to which it relates.

[redacted]

10/11/72

MEDICINES ACTS 1968 AND 1971

Product Licence of Right No. 0053 / 5019 TO 5038

SCHEDULE

Part 2 - FURTHER PROVISIONS SUBJECT TO WHICH THE LICENCE HAS BEEN GRANTED

1. The pharmaceutical form and active constituents of each description of product shall be in accordance with the particulars set out in the application to which Part 1 of this Schedule refers.

2. The constituents other than active constituents of each product shall be those specified in the said application or such others as may from time to time be approved by the licensing authority.

3. The products shall be sold or supplied for the purposes specified in the said application in accordance with the particulars given therein as to -

   (a) indications,
   (b) methods and routes of administration,
   (c) recommended dose or dosage,
   (d) directions, contra indications or warnings, and
   (e) methods of sale or supply,

   except in so far as may from time to time be approved by the licensing authority.

4. The products shall be manufactured by the person or persons named in the said application, or by any other person in the United Kingdom who may lawfully manufacture products of that description and whose name has been notified to the licensing authority by the holder of the licence.

5. The holder of the licence shall secure that the manufacturer of the products to which this licence relates shall permit the premises where they are manufactured and the operations carried on in the course of manufacturing them to be inspected by, or on behalf of, the licensing authority.

6. All the provisions of Part I of Schedule 1 of the Medicines (Standard Provisions for Licences and Certificates) Regulations 1971 (S.I.1971 No.972) shall apply.

[redacted]

10/11/72

Hmxhl3

PRODUCT LICENCE OF RIGHT No. 0109/5000

Application for
Product Licence of Right

AMENORONE

To

Department of Health and Social Security

Medicines Division

ROUSSEL

PRODUCT LICE[illegible] No. 0109/5000.

APPLICATION FOR PRODUCT LICENCE OF RIGHT

AMENORONE

PRODUCT LICENCE OF RIGHT No. 0109/5000

2. Licensee

ROUSSEL LABORATORIES LTD.,
ROUSSEL HOUSE,
NORTH END ROAD,
WEMBLEY,
MIDDLESEX HA9 ONF.

Telephone: 01-903 1454

PRODUCT LICENCE OF RIGHT No. 0109/5000

3. The licensee is responsible for the composition of the product.

PRODUCT LICENCE OF RIGHT No. 0104/5000

4. Not applicable.

PRODUCT LICENCE OF RIGHT No. 0109/5000

6. Activities to be covered by the licence

(a) Selling and supplying the product in the United Kingdom,

and

(b) Exporting the product from the United Kingdom.

PRODUCT LICENCE OF RIGHT No. 0109/5000

7. Product

AMENORONE

8. Pharmaceutical form

Amenorone is produced in tablet form only.

a) In a form for administration to human beings.

9. Composition

(a) Active ingredients

Ethinyloestradiol B.P.	0.01 mg.
Ethisterone B.P.	10 mg.

(b) Other ingredients

Sucrose B.P.

Starch (Potato) B.P.

Acacia B.P.

Gelatin B.P.

Talc B.P.

Magnesium stearate B.P.

10. Physical characteristics

White biconvex tablets 7 mm. diameter.

Markings: One side inscribed 'A' and the other '$\frac{R}{L}$' with a breakline.

Disintegration: Not less than 15 minutes.

11. Indications for Use

(a) Recommended use

For the correction of disorders of menstruation, including menorrhagia, metrorrhagia, polymenorrhoea and hypomenorrhoea and for inducing menstruation in primary and longstanding secondary amenorrhoea.

(b) Route of administration

Buccal or sublingual absorption.

(c) Recommended dosage

(Post-pubertal women only)

4 tablets daily for 5 days.

For polymenorrhoea and amenorrhoea precede with a 16 day treatment of ethinyloestradiol.

12. Standard provisions

The product is manufactured in compliance with the standard provisions.

No exemption is requested.

13. Manufacture and assembly

(a) Aqueous granulation and compression.

(b) Roussel Laboratories Ltd.,
Kingfisher Drive,
Covingham, Swindon, Wiltshire.

Both manufacture and assembly.

(d) Roussel Laboratories Ltd.,
London Distribution Depot,
96 Queen's Drive,
Ealing, London, W.5.

A high security, purpose built establishment

fitted with temperature controls and burglar alarms.

PRODUCT LICENCE OF RIGHT No. 0104/5000

14. Quality control

(a) Yes - at both intermediate and finished stages.

(b) Mr. [redacted].

15. Containers

Amenorone tablets are presented in a 30 ml. cylindrical tablet bottle. The bottle is of amber glass and is sealed with a 28 mm. Jaycap.

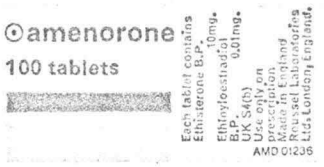
16. Labelling

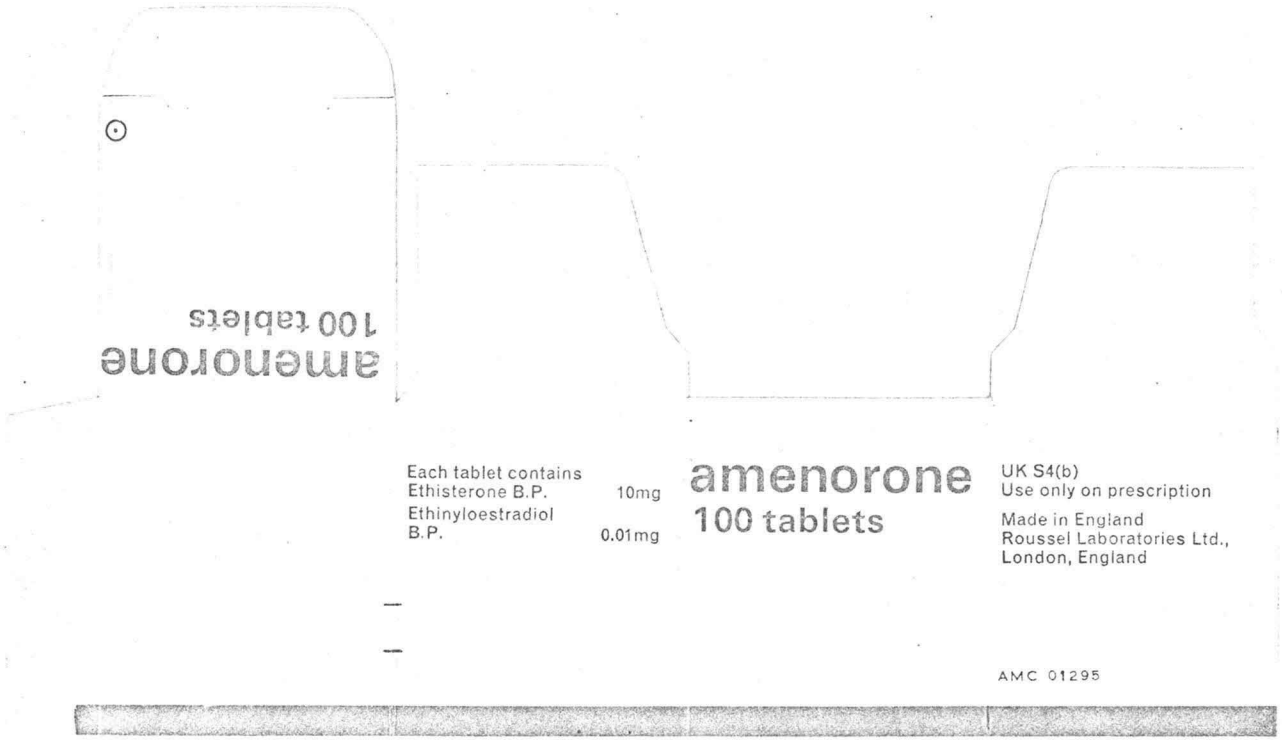
Samples of the carton and label are enclosed.

APPLICATION FOR A PRODUCT LICENCE OF RIGHT

PRODUCT LICENCE OF RIGHT No. 0169/5000

ROUSSEL LABORATORIES LIMITED





March, 1972.

17. Method of sale and supply

This product was made available before 1st September, 1971, as indicated:-

(b) (ii) Sold through registered pharmacies as a prescription item.

(c) Also through hospitals.

Evidence to support this statement can be found in the M. I. M. S. Annual Compendium, 1971.

PRODUCT LICENCE SUPPLEMENT No. 0109/5000

18. Therapeutic Substances Act and Diseases of Animals Act (Therapeutic Substances Order) Licences

Not applicable.

PRODUCT LICENCE OF RIGHT No. 0109/5000

We hereby apply for a Product Licence of Right in respect of

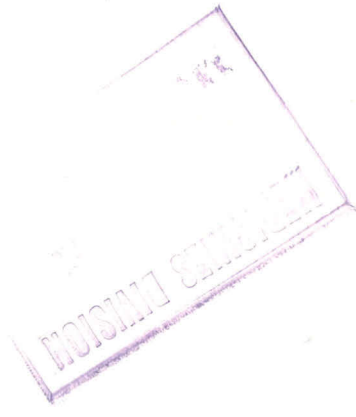
AMENORONE.

For and on behalf of ROUSSEL LABORATORIES LTD.

[redacted], F.R.I.C.

Director

31 May, 1972



Licence Nos. 0109/5000 To 5002
AND 5007 To 5021

MEDICINES ACTS 1968 AND 1971

A **PRODUCT LICENCE OF RIGHT** has been granted under and subject to the provisions of the Medicines Acts 1968 and 1971 to

ROUSSEL LABORATORIES LTD
ROUSSEL HOUSE
NORTH END ROAD
WEMBLEY
MIDDLESEX HA9 0NF

to authorise the dealings described in Part 1 of the attached Schedule in the products and under the licence numbers therein specified. The licence is subject to the further provisions set out or referred to in Part 2 of the said Schedule.

The licence, unless previously suspended, revoked or varied as to the period of its validity, shall continue in force until the end of a period of five years from the date on which it was granted.

Date granted : 6 APRIL 1973

A person authorised to [redacted] sign on behalf of the Secretary of State for Social Services.

6 APRIL 1973

Department of Health and Social Security,
Finsbury Square House,
33/37A, Finsbury Square,
London, E.C.2.

NOTICE

The existence of a product licence of right in respect of a particular product does not imply that the safety, quality or efficacy of the product has been considered by the licensing authority.

Under section 25 of the Medicines Act 1968 the licensing authority is required to grant such a licence to any applicant who proves that he fulfils certain conditions as to his dealings in the product before 1 September 1971. The licensing authority has power, normally after consulting the appropriate committee, to suspend, revoke or vary such a licence on specified grounds, which include considerations of safety, quality or efficacy.

After a date to be fixed by statutory order under Section 52 of the Medicines Act 1968, it will not be lawful (notwithstanding any provision in the relevant licence of right) to sell by retail any medicinal product otherwise than from a registered pharmacy unless the product is included on a general sale list or is covered by one of the statutory exemptions under sections 55 or 56 of the Act or by any exemption made by order under section 57 of the Act.

MEDICINES ACTS 1968 AND 1971

Product Licence of Right Nos. 0109 /5000 TO 5002 AND 5007 TO 5021

SCHEDULE

Part 1 - PARTICULARS OF THE DEALINGS, PRODUCTS AND LICENCE NUMBERS

1. The licence authorises the holder of the licence to sell or supply, or to procure the sale or supply, or to procure the manufacture or assembly for sale or supply of the products described in the holder's application dated 31 MAY 1972 and denoted on the attached copy by the respective licence numbers 0109 / 5000 TO 5002 AND 5007 TO 5021 under the product names set out therein and as the products of the holder of the licence.

2. The number so denoted shall be the licence number of the product to which it relates.

[redacted]

13473

MEDICINES ACTS 1968 AND 1971

Product Licence of Right Nos. 0109/5000 To 5002 AND 5007 To 5021

SCHEDULE

Part 2 - FURTHER PROVISIONS SUBJECT TO WHICH THE LICENCE HAS BEEN GRANTED

1. The pharmaceutical form and active constituents of each description of product shall be in accordance with the particulars set out in the application to which Part 1 of this Schedule refers.

2. The constituents other than active constituents of each product shall be those specified in the said application or such others as may from time to time be approved by the licensing authority.

3. The products shall be sold or supplied for the purposes specified in the said application in accordance with the particulars given therein as to -

   (a) indications,

   (b) methods and routes of administration,

   (c) recommended dose or dosage,

   (d) directions, contra indications or warnings, and

   (e) methods of sale or supply,

   except in so far as may from time to time be approved by the licensing authority.

4. The products shall be manufactured by the person or persons named in the said application, or by any other person in the United Kingdom licensed to manufacture products of that description and whose name has been notified to the licensing authority by the holder of the licence.

5. All the provisions of Part I of Schedule 1 of the Medicines (Standard Provisions for Licences and Certificates) Regulations 1971 (S.I. 1971 No. 972) shall apply.

[redacted]

3473

Box 3

PRODUCT LICENCE OF RIGHT No. 0109/5061

Application for
Product Licence of Right

AMENORONE FORTE

To

Department of Health and Social Security

Medicines Division

ROUSSEL

0109/5201

We hereby apply for a Product Licence of Right in respect of

AMENORONE FORTE.

For and on behalf of ROUSSEL LABORATORIES LTD,

[redacted] F.R.I.C.

Director

31 May, 1972

PRODUCT LICENCE OF RIGHT No. 0109/5001

APPLICATION FOR PRODUCT LICENCE OF RIGHT

AMENORONE FORTE

PRODUCT LICENCE OF RIGHT No. 0109/5001

1. Applicant

ROUSSEL LABORATORIES LTD.,
ROUSSEL HOUSE,
NORTH END ROAD,
WEMBLEY,
MIDDLESEX HA9 ONF.

Telephone: 01-903 1454

2. Licensee

ROUSSEL LABORATORIES LTD.,
ROUSSEL HOUSE,
NORTH END ROAD,
WEMBLEY,
MIDDLESEX HA9 ONF.

Telephone: 01-903 1454

3. The licensee is responsible for the composition of the product.

4. Not applicable.

5. Validity

To run for a period of 5 years.

6. Activities to be covered by the licence

(a) Selling and supplying the product in the United Kingdom,

and

(b) Exporting the product from the United Kingdom.

7. Product

AMENORONE FORTE

8. Pharmaceutical form

Amenorone Forte is made in tablet form only.

(a) In a form for administration to human beings.

9. Composition

(a) Active ingredients

Ethinyloestradiol B.P.	0.05 mg.
Ethisterone B.P.	50 mg.

(b) Other ingredients

Sucrose B.P.
Acacia B.P.
Gelatin B.P.
Magnesium stearate B.P.
Tragacanth B.P.
Orangeal essence No. 18551

10. Physical characteristics

White biconvex tablets 10 mm. diameter.

Markings: One side inscribed '$\frac{A}{F}$' ;
the other '$\frac{R}{L}$' with a breakline.

Disintegration: Not less than 15 minutes.

11. Indications for Use

(a) Recommended use

As a pregnancy test and for recent cases of secondary amenorrhoea.

(b) Route of administration

Buccal or sublingual absorption.

(c) Recommended dosage

1 tablet daily for 3 days. In resistant cases a higher dose such as 2 or even 3 tablets daily for 3 or more days may be used.

12. Standard provisions

The product is manufactured in compliance with the standard provisions.

No exemption is requested.

13. Manufacture and assembly

(a) Aqueous granulation and compressing.

(b) Roussel Laboratories Ltd.,
Kingfisher Drive,
Covingham, Swindon, Wiltshire.

Both manufacture and assembly.

(c) Roussel Laboratories Ltd.,
London Distribution Depot,
96 Queen's Drive,
Ealing, London, W.5.

A high security, purpose built establishment fitted with temperature controls and burglar alarms.

14. Quality control

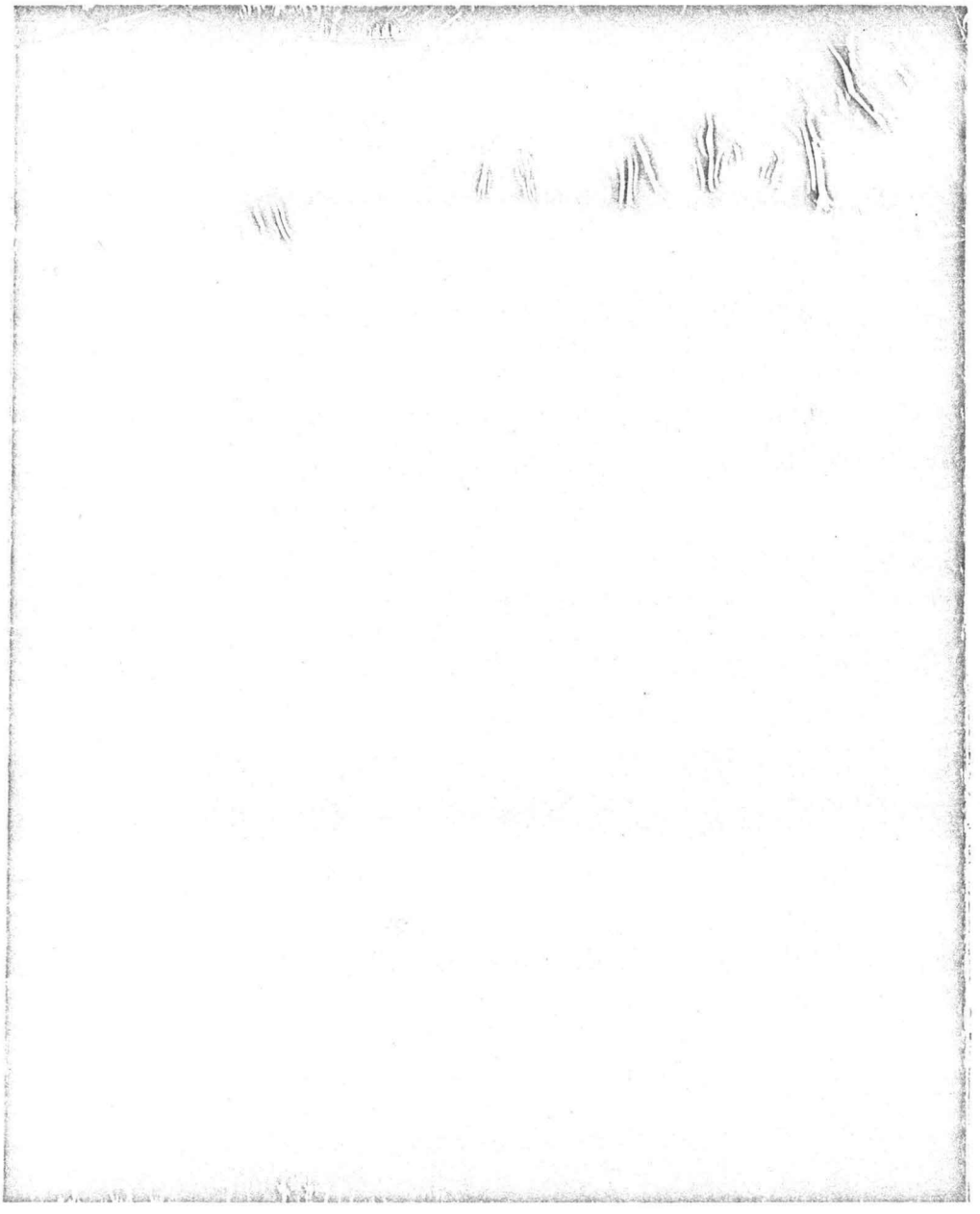
(a) Yes - at both intermediate and finished stages.

(b) Mr. [redacted]

15. Containers

Amenorone Forte tablets are packed in silver, plain aluminium foil.

A sample of this foil is provided.



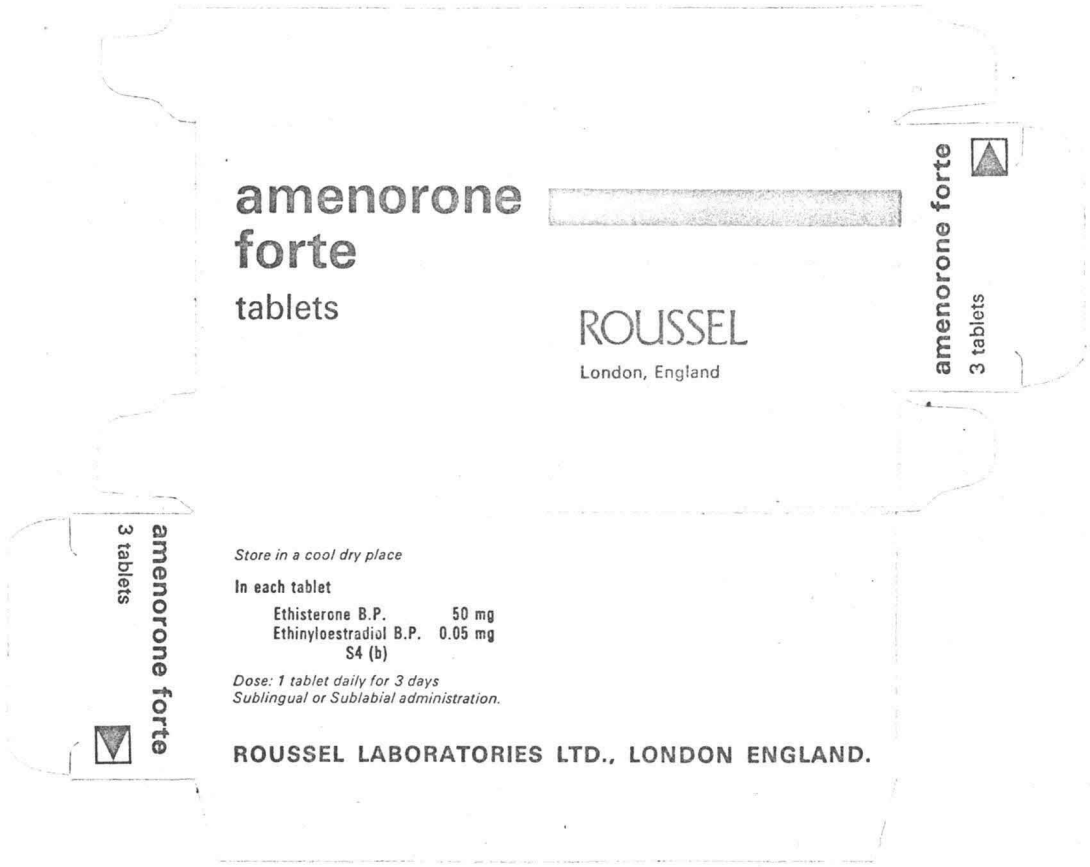
16. Labelling

A sample of the carton is attached.

PRODUCT LICENCE No. 0109/5001

APPLICATION FOR A PRODUCT LICENCE OF RIGHT

ROUSSEL LABORATORIES LIMITED



March, 1972.

17. Method of sale and supply

This product was made available before 1st September, 1971, as indicated:-

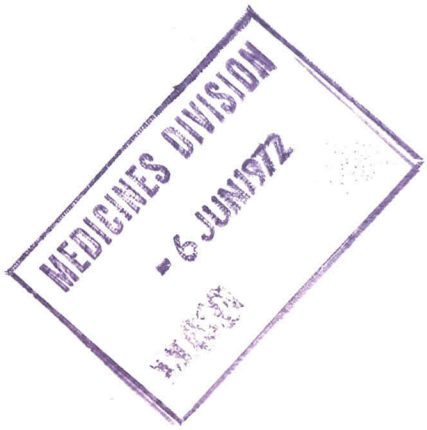
(b) (ii) Sold through registered pharmacies as a prescription item.

(c) Also through hospitals.

Evidence to support this statement can be found in the M. I. M. S. Annual Compendium, 1971.

18. Therapeutic Substances' Act and Diseases of Animals' Act (Therapeutic Substances Order) Licences

Not applicable.


MEDICINES DIVISION
- 6 JUNI 1972

ROUSSEL

Roussel Laboratories Ltd.
Roussel House · Wembley Park
Middlesex HA9 0NF · England
Registered Office

MAP/RR

27th November, 1973

Product Licence Section,
Medicines Division,
Department of Health & Social Security,
Finsbury Square House,
33-37A Finsbury Square,
LONDON EC2A 1PP

Dear Sirs,

PRODUCT LICENCE OF RIGHT 0109/5001
AMENORONE FORTE

We hereby request that our product licence of right for Amenorone Forte be varied with respect to the recommended use. We no longer wish to recommend this product as a pregnancy test and therefore the only indication will now be in recent cases of secondary amenorrhoea.

We enclose a newly prepared page 11 for our application, which should form part of your records if you accept this variation.

Y[redacted]

[redacted],
Head of Product Registration
and Information

Encl.

Phone: 01-903 1454
Telex: 23126
Cables: Labossel Wembley
Regd. London 336062

[redacted]

11. Indications for Use

(a) Recommended use

For recent cases of secondary amenorrhoea.

(b) Route of administration

Buccal or sublingual absorption.

(c) Recommended dosage

1 tablet daily for 3 days. In resistant cases a higher dose such as 2 or even 3 tablets daily for 3 or more days may be used.

Licence Nos. 0109/5000 To 5002
AND 5007 To 5021

MEDICINES ACTS 1968 AND 1971

A **PRODUCT LICENCE OF RIGHT** has been granted under and subject to the provisions of the Medicines Acts 1968 and 1971 to

ROUSSEL LABORATORIES LTD
ROUSSEL HOUSE
NORTH END ROAD
WEMBLEY
MIDDLESEX HA9 0NF

to authorise the dealings described in Part 1 of the attached Schedule in the products and under the licence numbers therein specified. The licence is subject to the further provisions set out or referred to in Part 2 of the said Schedule.

The licence, unless previously suspended, revoked or varied as to the period of its validity, shall continue in force until the end of a period of five years from the date on which it was granted.

Date granted : 6 APRIL 1973

A person authorised to sign on behalf of the Secretary of State for Social Services.

6 APRIL 1973

Department of Health and Social Security,
Finsbury Square House,
33/37A, Finsbury Square,
London, E.C.2.

NOTICE

The existence of a product licence of right in respect of a particular product does not imply that the safety, quality or efficacy of the product has been considered by the licensing authority.

Under section 25 of the Medicines Act 1968 the licensing authority is required to grant such a licence to any applicant who proves that he fulfils certain conditions as to his dealings in the product before 1 September 1971. The licensing authority has power, normally after consulting the appropriate committee, to suspend, revoke or vary such a licence on specified grounds, which include considerations of safety, quality or efficacy.

After a date to be fixed by statutory order under Section 52 of the Medicines Act 1968, it will not be lawful (notwithstanding any provision in the relevant licence of right) to sell by retail any medicinal product otherwise than from a registered pharmacy unless the product is included on a general sale list or is covered by one of the statutory exemptions under sections 55 or 56 of the Act or by any exemption made by order under section 57 of the Act.

MEDICINES ACTS 1968 AND 1971

Product Licence of Right Nos. 0109 /5000 TO 5002 AND 5007 TO 5021

SCHEDULE

Part 1 - PARTICULARS OF THE DEALINGS, PRODUCTS AND LICENCE NUMBERS

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2. The number so denoted shall be the licence number of the product to which it relates.

[redacted]

13473

MEDICINES ACTS 1968 AND 1971

Product Licence of Right Nos. 0109/5000 To 5002
AND 5007 To 5021

SCHEDULE

Part 2 - FURTHER PROVISIONS SUBJECT TO WHICH THE LICENCE HAS BEEN GRANTED

1. The pharmaceutical form and active constituents of each description of product shall be in accordance with the particulars set out in the application to which Part 1 of this Schedule refers.

2. The constituents other than active constituents of each product shall be those specified in the said application or such others as may from time to time be approved by the licensing authority.

3. The products shall be sold or supplied for the purposes specified in the said application in accordance with the particulars given therein as to -

   (a) indications,

   (b) methods and routes of administration,

   (c) recommended dose or dosage,

   (d) directions, contra indications or warnings, and

   (e) methods of sale or supply,

   except in so far as may from time to time be approved by the licensing authority.

4. The products shall be manufactured by the person or persons named in the said application, or by any other person in the United Kingdom licensed to manufacture products of that description and whose name has been notified to the licensing authority by the holder of the licence.

5. All the provisions of Part I of Schedule 1 of the Medicines (Standard Provisions for Licences and Certificates) Regulations 1971 (S.I. 1971 No. 972) shall apply.

[redacted]
3473

NHS Digital

COI:

NHS Digital is a Public Body established by statute (Health and Social Care Act 2012). Our remit is the provision of information infrastructure, systems and services to the whole health and care system in England. At an organisational level we have as a consequence of this remit, relationships and interests in every part of the public and private health and care domains. It would not be possible to document these relationships at an organisational level.

In terms of significant individuals i.e. members of the Board or Executive team, all employees are required to declare specific interests and potential conflicts of interest in accordance with our CoI policy.

Background

NHS Digital is an Executive Non-Departmental Public Body whose statutory basis powers and duties are set out in the Health and Social Care Act 2012. Our vision is to harness the power of information and technology to improve health and care. We supply information and data to the health service, provide vital digital technologies and infrastructure, and through our standards work help different parts of health and care work together. We are the guardians of patient data, making sure that it is protected, and only used for the good of health and care. We advise the health and care system on cyber and data security.

We are actively involved in two of your three subjects of interest and have described our roles under the relevant header, We have also answered your questions to the best of our ability

Areas of interest

Hormone Pregnancy Tests including Primodos

No current involvement

Sodium valproate and other valproate medications for women of child bearing age

NHS Digital through its primary care and clinical safety teams has worked with MHRA and DHSC to agree and implement GP IT systems with the necessary functionality to support the appropriate safeguards to women of child bearing age who are taking sodium valproate and other valproates. {More detail can be obtained from [redacted]

Synthetic mesh for use in abdominal and vaginal pelvic mesh procedures

NHS Digital has helped NHS England establish the size and complexity of this issue through its Data Insight and Statistics directorate. More detail can be provided from [redacted]

1. Please can you provide details of your relevant policies and protocols, if any, for ensuring that information relevant to patient safety, and learning from adverse events is disseminated amongst NHS organisations and beyond.

a) NHS Digital is responsible for the two current safety standards concerned with digital technology development and deployment in the NHS. This now includes medical devices which are software or which have software embedded, as the original scope excluded medical devices. This scope has been extended with full support of the MHRA. For further information please contact [redacted]
b) NHS Digital would use the central alerting system to promulgate relevant safety information
c) NHS Digital is responsible for leading and managing incidents which may be safety related for infrastructure and applications which it delivers on behalf of the health and care system. It also has a leadership role for managing suppliers when it manages national contracts on behalf of DHSC or NHS England or both. In this function it makes sure each incident not only resolves the technical failure but also ensures the duty of care on affected patients is also met. It works with partners, MHRA, NHS England, DHSC, PHE etc to ensure the correct process is followed and the relevant statutory roles are fulfilled. For further information please contact [redacted]
d) Through the Clinical Safety Group lead [redacted] we link to the national director for patient safety in NHS Improvement. The NHS Digital clinical safety team is working with NHSI who share their issues log with us when a they are linked to health IT and this includes medication risks and errors
e) We have with NHS England communicated to all CCGs and General Practices concerning the creation of local templates for data collection in GP system by IT specialists without specialist knowledge resulting in disruption of decision support tools

2. In your view, where within the healthcare system does your responsibility for disseminating adverse event reporting begin and end?

Our accountability and responsibility is limited to IT systems we either contract for on behalf of SoS or NHS England or infrastructure and national applications NHS Digital deploys in the health and social care system. In these circumstances NHS Digital would report any clinical incidents in 'live' systems to the National Service Desk, who in turn would involve the Service Bridge (NHS Digital) in investigating the issue to resolution and providing a route cause analysis. The clinician would remain actively involved in any incident reported, until such resolution is achieved and to support any remedial action that is required to minimise risk to the patient(s)

Part of NHS Digital's role is to facilitate better and more consistent, analysable data by driving digitalisation, standards and interoperability. This could play a role in recognising, collating and analysing adverse event in partnership with other stakeholders. In managing a register on behalf of NHS England or SoS we would be able to disseminate directly with patients and/or clinicians subject to the degree which the service was commissioned. An example of this would be the Breast Implant Registry we run. For further information please contact [redacted]

Finally NHS Digital runs a Trust System Support Model when local NHS Trusts can request NHS Digital expertise supports them in a difficult digital transformation problem. The responsibility and accountability for the remediation sits firmly and squarely with the NHS Trust. Should NHS Digital have concerns about capacity and capability it remains open to have an escalation route to NHS Improvement.

Outside of NHS Digital, our clinicians would report clinical safety issues through several avenues. Medication related issues may be reported to the MHRA using the yellow card system. Other

adverse events are often reported internally through local pathways individual to trusts/organisations e.g. DATIX.

3.How are you working with the private health care industry to develop a holistic picture of patient safety, specifically in relation to mesh? What would need to be put in place for this to happen? What is the time frame for delivery?

NHS Digital has a series of projects and programmes that work alongside frontline NHS organisations. Whilst not working directly with much of the private health care industry, the organisation does work with a variety of system providers, to ensure that systems are clinically safe and effective prior to approval and roll-out.

NHS Digital is working through the International Standards Organisation [ISO] with public and private partners to develop the next suite of international safety standards and hold the chair of at least one group. For further information contact [redacted]about the deliverables in 2019 and 2020 [redacted]

NHS Digital is working closely with MHRA to provide specialist input to support the Medical Devices Regulation due for full implementation on May 25th 2020. For further information please contact [redacted]

4.Do you think exisiting patient information held by the NHS could be used to identify and support at risk patient cohorts?

NHS Digital recognises that at present there are large reserves of inefficiently handled data within the NHS, which could be better used to identify key issues including at risk patient cohorts from medications eg indomethacin, medical devices including implants and diseases eg Kawasaki Disease. Many of our domains are working towards improving the way that data is collected, analysed and utilised, to improve patient care, but exploitation of this data requires either data dissemination to an interested party for research and innovation or specific commissions for NHS Digital to undertake work.

At present, issues remain around a lack of digitalisation and standardisation. Diverse clinical and coding systems create disparate pools of data, which can often lead to the duplication of large amounts of data. The ongoing use of paper forms and records also prevent the most effective method for collation and analysis of patient data. This is especially true in secondary care, where improvements in technology have been slower.

Assuming at risk cohorts can be identified which meets the systemic desirability test, there is an additional step of practical feasibility ie the staff and resources able to be diverted to manage those risks and either the stopping of other clinical work or the funding of new commissions.

We suggest you explore your main areas of interest with [redacted] and [redacted] whose details we have given above.

5.Can the Pregnancy Prevention Plan be built into the prescribing system for GPs and other prescribers? Is this currently being used for other medications?

NHS Digital holds contracts with several systems providers for GPs, many of whom already incorporate a functionality to alert the user of certain medication risks. This is often via pop-up alerts, which are generated for specific medications, this includes warnings on sodium valproate in women of child-bearing age.

Whilst the possibility of building the Pregnancy Prevention Plan into GP prescribing systems would therefore be possible, this would be best achieved by the creation of an NHS mandate, meaning that suppliers would have to incorporate this service into their systems. NHS Digital would then be able to work with suppliers to deliver this service in a safe and effective way.

The best or optimum method of integrating the Pregnancy Prevention Plan, alerts and decision support for new and repeat prescribing by GPs was fully investigated and discussed by the NHS Digital primary care and clinical safety group leads namely Dr Peter Short and Dr Manpreet Pujara and the MHRA leads for this activity to agree the optimum way forward. As a blueprint for going forward a dialogue with Peter and Manpreet may give the review a better insight into the complex clinical, workflow and behavioural changes that culminated in the agreed way forward especially as the role of neurologists was also key to successful implementation [redacted] and [redacted]

6. The Review has a broad remit including a focus on patient safety. Based on your experiences in developing and delivering registries as the Clinical Audits and Registries Management Service, in particular the Breast and Cosmetic Implant Registry, National Pulmonary Hypertension Audit, Out of Area Placements, any information you wished to contribute on running a registry, in particular the use of registry data in vigilance, would be welcome.

There are currently hundreds of registries across the health and social care system, some are standalone some are publicly funded, some are privately funded and some have components of each. The purpose of each commissioned registry is different some are used for audit, others research and others safety monitoring. The technical infrastructure, legal basis and utility of each is very different.

We think national registries should be aligned to national priorities and national funding. A partnership approach is the preferred model with virtual access to a central database being favoured over transfer of large data sets around the health and social care system with duplicate or inefficient funding. Monitoring should be as automated as possible and exploration and enhancement should be the main use of 3rd sector monies rather than managing and setting up the technical infrastructure of registries ie focused on the value added activities which attract donations.

For a more detailed dialogue we suggest you contact [redacted] and [redacted] whose details have already been given

There are some practical and technical issues that merit exploration for example the Breast Implant Registry (BIR) to provide implants with SNOMED codes. BIR do not currently use any unique identifiers. They ask for GTIN, but this is entered as a free text field, a method prone to errors. This is an area that clearly needs further work relating to standardisation and the ability to scan unique identifiers, as well as join registries together. In short the speed and affordability of set up of

registries will be greatly helped by standardisation most notably the use of common data standards, which could enable complex data sets needed for a comprehensive and granular registry to be built. In addition when things go wrong there needs to be a way of tracking the supply chain using GMDN &/or SNOMED CT standards with bar coding and linking that with the demand chain of detailed electronic patient records including for example the removal or abandoned surgical procedures [ie the person no longer has the deficient medical device]. For a deeper insight into the ontological core needed for linkage of data sets [redacted] would be a helpful addition to [redacted] and [redacted]

7. How could device traceability be improved? What technology would need to be in place to enable this? How would a registry assist with this process?

Ideally the work by the Scan4Safety team would be continued, so that devices scanned would automatically be entered into a centralised patient record. Previously with pelvic meshes and breast implants, there was little in the way of consistent record keeping – stickers would often be placed in patient notes, but this information would be difficult to retrieve and there was no centralisation. There are currently discussions regarding a Scan4Safety devices data pool and national registries.

NHS Digital is currently working towards the introduction of medication barcodes as part of the Falsifying Medicines Directive. This work could also be considered alongside that done by the Scan4Safety team, further highlighting the importance of unique identifiers. NHS Digital would have to investigate further alongside other teams who are leading on theses services.

As in the previous section we would recommend you have a dialogue with [redacted], [redacted] and [redacted] if you would like to explore this area more thorough both from sound record perspective to support research but also a safety incident that requires managing [[redacted]]

8. How could emerging technologies be used to support patient and physician reporting of adverse events and signal detection

Using power of digitalisation more effectively – electronic prescribing systems that allows clinical decision support to make the links and flags for signal detection, automated (or semi-automated) reporting mechanisms which in turn will reduce the burden placed on clinicians. Effectively using technology to make it easier for clinicians to report, detect patterns and use of 'big data'. Possibly machine intelligence (AI) could play a role here. Creating Apps and embedding the yellow card into systems such as EPR or EPMA while utilising clinical decision support within system suppliers or leverage external database suppliers such as First Databank. It should be noted the yellow card digital reporting standard is already approved

By using the power of digitalisation, both patients and healthcare providers would be empowered to more effectively report adverse outcomes. Some ideas for this would include:

- Automated (or semi-automated) reporting mechanisms that reduce the burden placed onto clinicians.
- The possible role of artificial intelligence (AI) in highlighting risk profiles and patterns of unfavourable outcomes.
- Patient-centred apps or wearables that allow collection or reporting of adverse outcomes. An example of this would be the MyCareCentric Epilepsy Programme, which equips patients with a wearable device to help self-manage their condition. The wearable collects data, can

classify seizure type, alert clinicians allowing real-time remote consultations and provide lifestyle recommendations and drug prescriptions.
- Embedding the yellow-card scheme into systems such as EPR or EPMA, allowing faster and easier adverse outcome reporting.
- Better collection and use of 'big data', allowing a greater understanding of risk profiles and the events leading up to adverse events.
- Creating partnerships and leveraging external database suppliers such as First Databank to further improve our collection and utilisation of health data.

NHS App team working with MHRA on patient self reporting of adverse events (Yellow card scheme). This is very recent as we only introduced them two weeks ago

Currently empowering the patient to contribute to the NHS [ie it is not what the NHS can do for you it is what you can do for the NHS] is the most under-utilised tool for clinical safety. If the NHS were to enable a market whereby patients can have their own Personal Health Records it would become a piece of essential infrastructure. A PHR would be able to process:

A] Copies of individual registered provider records from health and social care publicly provided care. This includes health and social care

B] Copies of individual registered provider records from health and social care privately provided care . This includes health and social care

C] Data from self purchased apps and devices aimed at physiological measurement and/or well being

D] Other data which may be significant in health and well being, examples include shopping data which may point to alcohol ingestion, social interests eg on line gambling which may be a manifestation of addiction or a side effect of treatment eg dopamine againists in Parkinson's disease

With patient empowerment applications could be built on the PHR platform for example medications that need monitoring by blood tests, eye tests and/or imaging through giving them the request forms and in addition having the results sent to them in their PHR so patients de-facto monitor themselves and save on appointments and "what are my results ?" phone calls, the creation of unnecessary stress and potentially reduce litigation. For further information please contact [redacted] [redacted]]

9. What further systems would we need to have in place to capture information to improve patient safety and adverse event reporting

All devices need to be GS1 compliant, system suppliers need to have solutions which can scan and track products, but also have adequate security and a robust reporting functionality to allow the data to be effectively mined. A review of the electronic yellow card scheme could take place to consider the inclusion of medicines and devices, in all IT systems not just GO IT systems.

The prescriber of a medical device with software embedded which is to be used by patients comes with a clinical requirement that the patient can use it successfully and safely. This implies that the following should be seriously considered:

- The device can be prescribed and the data managed according to NHS standards
- The patient can be trained to use the device soundly

- Medical insurance and CNST must indemnify clinicians and providers for medical device prescribing for patients
- Data from medical devices must go to the patient and the prescriber so a platform that links patients, provider and device is crucial
- Medical device outputs need to be mapped to NHS data standards like SNOMED CT so the data can be seamlessly incorporated into the record
- Medical devices which constantly monitoring should go through an intermediate digital service which graphs the results and shows normal ranges so the information can be more easily consumed by patients and clinicians
- Medical devices integrated into provider systems should be deemed safe in those environments through meeting the safety standard for deployment
- Clinician decision support tools should be tested for extensibility and generalisability before national roll out and prevent errors
- Manufacturers and their clinicians should understand what is and what is not a medical device and have medical devices registered and regulated by MHRA
- Every piece of software that is to be used by or on patients for their care should have a responsible clinician named akin to the consultant name on the bed so that all complaints, audits, quality improvements service upgrades etc are analysed through the clinical safety lens

To explore this further [redacted] and [redacted] should be contacted using details described above.

NHS England

COI:

NHS England is a publicly funded body and is in no part commercially funded. Staff abide by the Standards of Business Conduct policy: https://www.england.nhs.uk/publication/standards-of-business-conduct-policy/

Submission:

Q1. Please could you provide a timeline outlining your understanding and recognition of risks regarding the interventions covered by this Review.
This may include: initial recognition of the risk, dates of consequential and significant research studies, reports raised directly to, and actions taken by, NHS England, and communication of regulatory and professional guidance to clinicians and patients.

The MHRA's letter in Annex A sets out guidance on the handling of valproate issues. NHS England is involved in the valproate stakeholder network which supports clinical review of patients and suggests alternatives for those at risk.

The timeline with respect to abdominal and vaginal pelvic mesh procedures is set out below:

2015
NHS England set up a Mesh Working Group to address concerns around the safety and efficacy of surgery for stress urinary incontinence (SUI) and pelvic organ prolapse (POP), using mesh devices. The Working Group published its Interim Report in 2015 which set out recommendations to optimise care for women undergoing treatment for SUI and POP.

2016/17
During 2016/17 the Mesh Oversight Group (Terms of Reference at Annex B) ensured that the recommendations of the interim report were implemented working alongside the British Society of Urogynaecology (BSUG); British Association of Urological Surgeons (BAUS); the Royal College of Obstetricians and Gynaecologists (RCOG), and the Medicines and Healthcare products Regulatory Agency (MHRA), National Institute for Health and Care Excellence (NICE), the Department of Health & Social Care (DHSC) and of patient members. The Mesh Oversight Group report sets out the actions that have been taken to fulfil those recommendations including improvements to:

- The clinical quality of the care women receive including improvements to surgical practice and training, updating of clinical guidance and standards, raising awareness of post-operative problems amongst GPs and offering improved and swifter access to clinical expertise for women with post-operative problems.
- The quality and amount of data and information available to support informed decision making by patients and clinicians. This includes improving the reporting of adverse incidents and improving procedure coding in Hospital Episode Statistics so that a more complete picture of the level and seriousness of complications is established.
- The consent process so women are more aware of the pros and cons of the treatment option they have chosen or agreed to. For example through the provision of high quality standardised information for patients and a more consistent consent process.

The final mesh report summarises the actions that have been taken to fulfil those recommendations and is available from our website. https://www.england.nhs.uk/mesh/

Two comprehensive patient information leaflets have now been produced in collaboration with the Independent Review of Transvaginal Mesh Implants working group for Scotland. The leaflets provide information about SUI and POP procedures, surgical alternatives to mesh, non-surgical alternatives to surgery and risk and complications of procedures.

Surgical Procedures for Treatment of Pelvic Organ Prolapse in Women

Synthetic Vaginal Mesh Tape Procedure for the Surgical Treatment of Stress Urinary Incontinence in Women

A learning resource for GPs was commissioned by NHS England so women who see their GP with mesh complications receive the appropriate support and are swiftly referred to self-declared centres where necessary.

2018
As part of recommendations from the MESH working group, NHS Digital released a publication on 17 April 2018, reviewing Hospital Episode Statistics (HES) data on surgery for urogynaecological prolapse and stress incontinence using tape or mesh. https://digital.nhs.uk/news-and-events/latest-news/nhs-digital-publishes-statistics-on-vaginal-mesh-procedures

The Chief Medical Officer accepted the recommendations of the Mesh Oversight Group in full and with immediate effect. Annex C describes the actions which were sent out to Regional Directors, Trust Medical Directors, and clinicians involved in the care of patients with stress urinary incontinence and pelvic organ prolapse.

Q2. Please provide an appropriately anonymised summary of patient or other concerns raised directly with NHS England over time regarding hormonal pregnancy tests, sodium valproate, and pelvic mesh.

Summary of enquiries we have received on mesh since September 2014 according to our records. These include correspondence and parliamentary questions.

- Enquiries received:
    - 1 in 14-15
    - 11 in 15-16
    - 7 in 17-18
    - 8 in the current year.

Themes of enquiries cover:

- criticism of the clinical procedures used;
- complications and pain following surgery;
- delays to remedial clinical procedures;
- the certification of mesh surgeons; and
- information available to patients on the risks of mesh.

Q3. With regard to the Mesh Oversight Group can you describe its: rationale, role and function; and next steps.

The Mesh Oversight Group Terms of Reference can be found at Annex B

Q4. What services and schemes are available to support those with longterm health conditions as a result of adverse surgical outcomes, or exposure to teratogenic medications in utero? Can you briefly describe how these are administered and accessed by those affected? What proportion of those affected do you estimate are able to access these services?

Local commissioners are responsible for ensuring appropriate services are available to their patients and that those services are tailored to the needs of the population.

Q5. How does NHSE interact with other organisations, regulators, and practitioners with regards to patient safety and adverse events. Where do its specific responsibilities lie?

NHS England works closely with NHS Improvement, which is responsible for strategic patient safety, and other partners. Please refer to NHS Improvement for an overview.

Q6. How does NHS England work with other Arm's Length Bodies of the Department of Health and Social Care in regards to:

a) User experience and complaints;

In the case of valproate, the Chief Pharmaceutical Officer, based in NHS England, has worked with MHRA and other partners to act on concerns.

With regards to vaginal mesh, the NHS England-led MESH working group was formed in response to issues raised by patient organisations and some clinicians around harm resulting from mesh implants. Three sub-working groups were subsequently developed with the aim of establishing the evidence around, and improving processes with regards: data and information; clinical quality; and informed consent.

One of the main objectives of the working group was to identify the evidence around use of vaginal mesh and understand other pertinent information from regulatory agencies (MHRA).

NHS England's role in the MESH working group, chaired by Keith Willett, was to act as a broker to open and honest debate between patients, clinicians, policy makers and regulators. In 2015, key recommendations were made by the working group, via a report to clinicians, regulatory agencies and other NHS arms–length bodies, including NICE.
Stakeholders included: British Society of uro-gynaecology (BSUG), Medicines and Healthcare Products Regulatory Agency MHRA, British Association of urological Surgeons (BAUS), Department of Health (DH) and patient groups.

Stakeholders were involved from the outset and instigated the report. Sub-groups were set up for each of following areas: Clinical Quality, Data and Information and Informed Consent. The sub groups were made of members from the Working Group and selected other people with relevant expertise or experience.

b) adverse events and warning signals; and

Responsibility for cross-system patient safety including adverse events and warning signals, sits with NHS Improvement with whom NHS England works closely.

c) education, training and guidance of healthcare professionals in light of emerging risks and adoption of new clinical approaches, medicines and medical devices?

Whilst guidance has been provided to clinicians on the use of mesh, in general NHS England is not responsible for the education and training of healthcare professionals. It may be helpful to refer to

Health Education England on this question. NHS England provides advice and input to NICE which develops clinical guidance for the NHS.

Q7. Do drug adverse events fall under the Serious Incidents Framework? If not, what framework would cover this?

Please refer to NHS Improvement which is responsible for the Serious Incidents Framework.

Q8. Do you consider your organisation to be proactive or reactive in regards to identifying and learning from adverse events? How do you demonstrate this? What use is made of social media?

Please refer to NHS Improvement which is responsible for identifying and learning in the context of strategic patient safety.

Q9. How does NHS England use patient complaints, including adverse event reporting, to improve services and quality of care?

Work is continuing to ensure that feedback is used to help support delivery and improve patient safety and policy development and review. At a national level we have undertaken specific reviews into complaints and this information has been fed back to relevant policy teams and learning and intelligence is fed back to the oversight group. We have also made changes to our data systems so that learning can more easily be identified and extracted from the system. At a local level intelligence from complaints and other forms of feedback is fed into the local assurance and review processes including local quality assurance meetings. We have also engaged with other arms-length bodies to start to develop processes to help share intelligence.

Q10. Please can you provide details of your relevant policies and protocols, if any, for ensuring that information relevant to patient safety, and learning from adverse events is disseminated amongst NHS organisations and beyond.

NHS England disseminates guidance to its networks and stakeholders where necessary, for example through Primary Care Networks, CCG and GP Bulletins and regional teams such as regional pharmacists or, where appropriate through joint communications from the Medical Directors of NHS England and NHS Improvement.

NHS England works in a coordinated way with other partners to ensure information is disseminated appropriately. For example in the contribution made by the Chief Pharmaceutical Officer to the valproate letter cascaded through the Central Alerting System (CAS) to clinical governance teams across the NHS.

On questions about learning systems for patient safety please refer to NHS Improvement.

Q11. How are examples of best practice and learning shared within the NHS organisation? What is the role of NHS England in co-ordinating this?

One example would be the issue of pelvic mesh where there has been significant progress. Information available to women and clinicians is now better and more consistent. Comprehensive information leaflets on treatment options for SUI and POP have been developed. A learning resource for GPs has also been created that uses what we have learned from our patient members about seeing and treating women who have received mesh implants.

Q12. What factors influence the decision on when to update guidance, and how are adverse events reports weighted in this process given the known level of underreporting?

Please refer to NHS Improvement which is responsible for the strategic patient safety function.

Q13. What guidance, if any, has NHS England provided to Trusts and Healthcare Professionals, on any of the three clinical interventions in the Scope of the Review? Please provide in chronological date order in relation to each intervention.

Please see Annex A which is a copy of the MHRA's valproate pregnancy prevention programme co-signed by the Chief Professional Officer, hosted by NHS England.

Please see Annex C for guidance on pelvic mesh.

Q14. What progress has been made in making patient record systems truly interoperable? What objectives have been set for the development of local/national healthcare information systems that fully reflect the patient journey (ie that link the patient to the procedure undertaken; the device implanted to the consultant; the GP to the relevant healthcare provider (NHS and/or private sector); and the patient outcome and/or any adverse event reports to all relevant clinicians and/or organisations). What is the time frame for achieving this? Will this include linkages between the NHS and the private sector, for example, if a device is implanted on the NHS and removed privately, how will this be recorded?

Please refer to NHS Digital which is best placed to answer questions about patient record systems and data linkage.

Q15. Are regulatory decisions made with reference to the data capture of any/ all existing UK registries? If not, why not? Do any of the registries currently in operation meet the standards set by the International Medical Device Regulators Forum or other internationally recognised standards? Please highlight those that do. For those that do not are you able to say what are the common missing elements?

Please refer to the Medicines and Healthcare products Regulatory Agency.

Q16. What advice can you share on establishing, accrediting and monitoring specialist clinical centres, and Centres of Excellence? What factors influence the establishment of these?

Not applicable to hormone pregnancy tests and valproate.

With regards to pelvic mesh, the national specialised commissioning team will develop, consult on, and publish a service specification for the centres providing an experienced team for mesh removal. This will include advice on referral, multidisciplinary assessment to consider mesh removal, and surgery by expert teams. There will be a procurement of a limited number of centres providing the balance between geographical access and maximising centre activity to rapidly build expertise. These centres will be linked by a national network to report their treatment outcomes.

NHS England's Complex Gynaecology Specialised Commissioning Team is also revising the service specifications of nationally commissioned services for complex gynaecology. These will ensure that NHS England commissions only those services able to demonstrate they meet the defined treatment and quality requirements. As experience develops in the specialised centres for mesh removal, as defined above, and evidence of treatment outcomes are reported, the commissioning team will consider the formation of national clinical policy supporting the pathway of care.

Q17. Looking to the future, what developments do you forsee in relation to:
a. adverse event monitoring and action;
Please refer to NHS Improvement which is responsible for the strategic patient safety function

b. registries; and
See the answer to question 18.

c. any other NHSE activities that are relevant to the Review.
See answer to question 1 and elsewhere in this response.

Q18. Please give a brief summary of the process and limitations to commissioning, and maintaining registries.

Registries for medical devices can perform a useful function in patient safety surveillance. For example the National Joint Registry monitors patient outcomes for joint replacements of hips, knees, ankles, elbows and shoulders and the vascular registry measures the quality of care for patients who undergo vascular procedures in NHS hospitals**.** The added value of these registries has been in the proactive tracking and analysis of the data so that early signs of failure can be detected. The establishment of a registry on its own, though, will not ensure patient safety. For example problems with metal on metal hip replacement in the mid-2000s were not picked up by registries initially, but by individual adverse incident reports. Registries may be seen to be most effective in ensuring patient safety when used as part of a programme of quality improvement.

The creation of lots of separate registries for every possible implant would be expensive. Instead it may be better to explore the development of data sets like the maternity services dataset (MSDS). With respect to the focus of this review, this might take the form of primary data standards for gynaecology (GDS) and a new secondary uses data set for gynaecology where providers would submit data regularly to NHS Digital. This approach is in line with the personal electronic health care record approach.

Establishing datasets would also have cost implications but the benefit of this approach is that the use of any new medicine or device is permanently integrated into the wider health record enabling the identification of long-term complications. The Review may wish to follow up with NHS Digital for further information.

ANNEX A: VALPROATE PREGNANCY PREVENTION PROGRAMME LETTER

Download here:
https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAttachment.aspx?Attachment_id=103118

ANNEX B: MESH OVERSIGHT GROUP Terms of Reference

MESH Oversight Group Terms of Reference

Context

The MESH programme so far represents a committed and collaborative piece of work borne out of the concerns of patients regarding the treatment of Stress Urinary Incontinence and Pelvic Organ Prolapse using MESH.

An interim report, published in December, has set out some thoughtful recommendations for implementation in 2016/2017; some led by NHS England but most led by external stakeholders. These same stakeholders are subject matter experts who have contributed to the development of the interim report.

The Acute Care Policy unit provide overall leadership and the secretariat for this work.

Purpose

This oversight group is tasked with:

1. Ensuring that the interim report's recommendations are implemented in a timely manner, according to the project plan.
2. Consideration of and consultation on risks and opportunities in order to influence successful implementation of the recommendations.
3. Having overview of progress reporting in order to support and facilitate high quality work.
4. Ratifying and validation the project plan, final report and key documents as they arise.

Scope

The oversight group will not be required to revisit work consulted on and completed so far. An exception will be to consider key research findings as they are published and account for them accordingly in the project plan, recommendations and final report.

The oversight group will consider new business, outside of the current recommendations, in order to successfully manage changes in POP and SUI practice using Mesh.

Membership

Organisation

RCOG

MHRA

BAUS

BSUG

DoH

NICE

NHSE

Patient members as required

Chair/ Co chair

Guiding principles

1. Action plans will be reviewed objectively and in a way that values the opinions of all stakeholders.
2. Action plans will use evidence and best practice to guide both content and methods of delivery.
3. Any additional work or recommendations should be agreed to be in scope by the oversight group.
4. Patient experience is an important determinant of the quality of care and shall continue to be sought out. This should be as agreed by the oversight group and in relation to specific and well defined action plan elements.
5. Members will be aware of the need for discretion and confidentiality when sensitive and unpublished matters are discussed.
6. Members will agree to disclosure of their position as a standing member of the oversight group as and when requested.

Governance and reporting

1. The oversight Group will be supported by more regular, business as usual, internal team meetings.
2. Highlight reports will be shared with the Maternity programme board and the Women's health patient safety group as required.

ANNEX C: Support for Medical Directors in assuring the competence of surgeons to carry out procedures from the 'high vigilance scrutiny' group from: Professor Keith Willett (NHSE) and Dr Kathy McLean (NHSI)

The Clinical Advisory Group guidance requires that the surgeon's competence in the procedure must be signed off in advance by the trust/hospital Medical Director as part of the high vigilance procedure. This should include a 'critical interview' exploring the surgeon's practice and supported by regular performance review, assessing evidence that the surgeon:

i. has been appropriately trained
ii. has actively maintained their skills
iii. has a record of their practice of the procedure, follow-up, and documented complications including mesh/tape removals
iv. is recording <u>every</u> procedure on the specialty database (BSUG, BAUS or TPFS) or any subsequently developed national recording system

The responsibility for this process lies with the trust Medical Director (MD). The MD may choose to deputise the practicalities of the process to the Clinical Director or a Consultant responsible for governance, who would then report back to the MD. As the MD is ultimately responsible, they must determine the exact methodology within their trust.

The following provides some suggested sources of information and evidence that Medical Directors may wish to take into account in order to support this process.

<u>The surgeon has been appropriately trained (i)</u>

1. Consultants who have completed subspecialty (specialist) training should have documented evidence of procedures that have been formally assessed.

2. Senior Consultants active in training and assessing trainees as competent to perform these procedures can be considered de facto to be evidenced as trained.

3. Some Consultants will have evidence of training outside of a training programme (such as letters confirming competency from a Consultant active in training).

4. In rare circumstances where none of the above applies, if the Medical Director is uncertain in making a judgement, they may ask a specialist society to recommend a recognised expert in the procedure to advise them.

<u>The surgeon has actively maintained their skills (ii)</u>

5. A record of the number of procedures performed is present in the surgeon's logbook, and in the procedure-coded HES data that trusts submit centrally.

6. Surgeons will have documentation of their annual appraisal.

7. Evidence of CPD collected as part of the appraisal process will demonstrate teaching performed, teaching received, and meetings attended. At least every 3 years, this CPD activity should include the subspecialty area in question.

8. Records of the surgeon's attendance for at least 70% of appropriate MDT meetings evidences active involvement in this process.

9. Again, in the event of uncertainty the Medical Director may request the name of a recognised expert from the specialist societies to advise them.

<u>The surgeon has a record of their practice of the procedure, follow-up, and documented complications including mesh/tape removals (iii)</u>

10. Surgeons will maintain a logbook of relevant procedures and of other procedures involving generic skills pertinent to the surgery in question.

11. Records of the procedures performed should also be held by the trust.

12. Significant complications should be discussed at 'Morbidity and Mortality' meetings.

13. All significant complications now require a duty of candour, and hence reporting to the local governance group - as such this data will be available for review.

14. We recommend that each unit should now submit 3-monthly returns to the Responsible Officer.

15. As above, if there are concerns as to whether a surgeon's evidence is sufficient for MD sign-off, then guidance could be sought through a specialist society.

<u>The surgeon is recording every procedure on the specialty database (BSUG, BAUS or TPFS) or any subsequently developed national recording system (iv)</u>

16. This is a new requirement. Surgeons who did not record procedures on these databases previously are not excluded from practice, but all procedures should be recorded from the initiation of the pause onwards.

17. Each surgeon may be asked to provide written assurance to the Responsible Officer committing that data for all patients will be entered onto a national database, except where the patient withholds consent. Trusts should provide administrative support to surgeons for this process.

18. Surgeons should collect summaries of audit data, both for their annual appraisal and at local level 3-monthly. This should correlate with records of activity to confirm 100% data entry compliance.

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https://www.improvement.nhs.uk

24 October 2018

Call for Evidence for the Independent Medicines and Medical Devices Safety Review

Response from NHS Improvement to request reference KGBBNE

A note on the term 'Adverse Events'

'Adverse events' is a term that is not widely used in current patient safety processes, as it may mean both adverse effects (i.e. side effects/harm from a medication or implant that has been used in line with required/established practice at that time) and error/mistakes (i.e. failing to follow current clinical guidance, giving a different drug/dose to the one intended, accidentally selecting a different implant to the intended implant, etc.). The remit of the patient safety team in NHS Improvement is focused on the latter.

To avoid the confusion that can be caused by the term 'adverse events' the patient safety team in NHS Improvement focus on 'patient safety incidents' which are defined as ''any unintended or unexpected incident (act of omission or commission) which could have, or did, lead to harm for one or more patients receiving healthcare.''

What is NHS Improvement?

NHS Improvement is responsible for overseeing foundation trusts and NHS trusts, as well as independent providers that provide NHS-funded care. NHS Improvement offers the support these providers need to give patients consistently safe, high quality, compassionate care within local health systems that are financially sustainable. By holding providers to account and, where necessary, intervening, NHS Improvement helps the NHS to meet its short-term challenges and secure its future. Formed on 1 April 2016, NHS Improvement is the operational name for an organisation that brings together: Monitor; NHS Trust Development Authority; and from NHS England, Intensive Support Teams, the Advancing Change Team and the national Patient Safety Team, including the National Reporting and Learning

System (NRLS), and archives from the National Patient Safety Agency (established in 2001 and abolished in 2012). NHS Improvement is legally responsible for delivering two statutory patient safety duties across the NHS, as per the Health and Social Care Act 2012, part 1, section 23, clause 13R, which includes:

- collecting information about what goes wrong in healthcare (currently fulfilled in large part by the NRLS); and
- using that information to provide advice and guidance "for the purposes of maintaining and improving the safety of the services provided by the health service"

Adverse events, clinical guidance and patient safety

The Medicines and Healthcare products Regulatory Agency (MHRA) is the lead agency for identifying and acting in relation to adverse effects associated with drugs and devices. Specifically, MHRA are concerned where adverse effects occur when the drug or device is used as intended. Yellow Card reporting to MHRA is the primary route for surveillance around the adverse effects of drugs and devices.

The National Institute for Health and Care Excellence (NICE) is the lead agency for developing and issuing more general clinical guidance in relation to the delivery of good quality healthcare. NHS England will also convene cross-ALB groups on specific issues around quality, particularly in relation to the domains of efficacy and patient experience.

The Patient Safety Team in NHS Improvement (and the functions of its predecessor agencies) are primarily focused on aspects of patient safety that are not already encompassed in the remits of existing regulatory or advisory bodies such as MHRA and NICE. The focus of the team is on learning from and reducing the risk of patient safety incidents and in particular acts, either omissions or commission, in the delivery of healthcare that could have or did lead to harm to one or more patients. In that sense the work of the NHS Improvement Patient Safety Team is distinguished from that of the MHRA as the Patient Safety Team focus on incident where people do not use drugs or devices as intended while the MHRA are focussed on events where drugs or devices are used as intended but harm occurs anyway.

The NRLS, developed by the National Patient Safety Agency in 2003, collects over two million patient safety incident reports per year across all care settings in England and Wales, most of which are voluntarily reported by NHS staff in Acute and Mental Health settings. NRLS incidents are clustered by location, type of incident, reported degree of harm, specialty and other categorical fields. The national distribution of the data within these clusters are made publicly available on biannual statistics publications (see Attachment A for more detail on the NRLS.)

Working together

NRLS data supports the work of other organisations such as the Care Quality Commission, Public Health England and MHRA, by sharing raw incident data in conformance with existing data sharing agreements between NHS Improvement and other parties. All patient safety incidents reported to the NRLS where incident types are classified as medication or devices incidents are shared monthly with MHRA to help in its regulatory role ensuring that medicines and medical devices work and are acceptably safe. This ensures that information

that is relevant to the remit of the other organisations reaches the right people regardless of the route through which it was reported.

The national Patient Safety Team also works regularly and closely with MHRA colleagues on specific issues found during routine review. This may range from simply handing on a patient safety issue, where it is felt that the issue lies within the regulatory remit of the MHRA, to more collaborative working where the issue is complex and cannot be fully resolved solely within the limits of the MHRA's existing legislative powers. In addition, there is a regular MHRA/NHS Improvement Patient Safety Team Partners meeting that allows discussion between the teams with respect to the effectiveness of the ongoing working relationship, and also covers those areas where there is joint ownership including the Medication Safety Officer and Medical Device Safety Officer networks.

NHS Improvement has been working closely with MHRA to ensure that any incidents recorded through the new Patient Safety Incident Management System (PSIMS) – which will replace the NRLS in 2019/20 - can be shared directly with MHRA to contribute to shared learning. This has involved a harmonisation of the newly redeveloped PSIMS taxonomy with a core set of the MHRA's Yellow Card reporting fields. Further, the new system aims to provide access to much more sophisticated searching and analysis tools than are currently available in the NRLS, making use of free-text analysis software to process the 'stories' of what goes wrong in healthcare and not just the categorical fields completed by reporters, so that "unknown unknowns" can be surfaced, without restriction to looking for what we already know causes problems. A Beta version of the new system will shortly be piloted in 20 providers across England and learning from this test phase will be used to refine the system further.

Review Questions and NHS Improvement Responses

1. Please could you provide a timeline outlining your understanding and recognition of risks regarding the interventions covered by this Review. This may include: initial recognition of the risk, dates of consequential and significant research studies, and communication of regulatory and professional guidance to clinicians and patients.

We understand the use of Primidos and similar hormonal pregnancy tests predates the existence of NHSI and the NPSA archive it holds. For vaginal mesh and for Sodium Valproate our involvement has primarily been through the data sharing, meetings and networks described above. Additionally, we supported the MHRA by issuing a co-badged Alert on Sodium valproate in April 2017 (see Attachment B MHRA & NHSI Valproate Alert). This did not include new guidance, but required a systematic approach by organisations, reinforcing the advice MHRA had previously directed to individual healthcare professionals.

2. How can adverse event data be used to promote patient safety and improve care?

See earlier note on the term 'adverse events'.

We support the MHRA through sharing NRLS data that will help enhance their ability to identify and quantify adverse effects of drugs and devices. We are developing PSIMS in

order to support MHRA's reporting requirements better (please see the information provided above). Having clear lead organisations with all bodies and teams sharing any relevant intelligence appears key

3. *Please can you provide details of your relevant policies and protocols, if any, for ensuring that information relevant to patient safety, and learning from adverse events is disseminated within NHS organisations and beyond.*

See earlier comments on the term 'adverse events'.

The following documents give a core summary of how we act, including through NHS Improvement Patient Safety Alerts. For more detailed information, see Attachment C Serious Incident Framework, Attachment D a recent Patient Safety Review and Response Report, and Attachments E & F for examples of recent NHS Improvement Alerts).

4. Where within the healthcare system does your responsibility for disseminating adverse event reporting and implementing evidence-based change begin and end?

Please see the general information provided above on how we share information with the MHRA, and the descriptions at the beginning of this paper on the distinction between adverse events and patient safety incidents and how we distinguish and the respective roles of MHRA, NICE and NHSI.

NHSI has recently taken on additional responsibilities in relation to improving the development and impact of Alerts issued via the Central Alerting System by all national bodies and teams with responsibilities for patient safety (including the MHRA, the Chief Medical Officer, NHS England, NHSI Patient Safety, NHSI Estates and facilities, DHSC Supply Disruption, NHS Digital, etc.)The Secretary of State for Health has asked the NHS National Director of Patient Safety to lead the development of systems for ensuring the NHS can clearly recognise Alerts requiring action to protect patients from the most serious risks, regardless of which safety body issues them. The work is being taken forward through a new National Patient Safety Alert Committee (NaPSAC) which will agree common standards, thresholds, and formats for National Patient Safety Alerts, and provide advice to CQC on inspecting compliance with these Alerts. This National Patient Safety Alert Committee (NaPSAC) will be responsible for ensuring the NHS can clearly recognise alerts requiring urgent action to protect patients from the most serious risks, regardless of which safety body issues them, including for cases of safety concerns about adverse effects from medicines or medical devices.

5. What role does clinical audit play in identifying adverse events? How is this information collated, communicated and shared? How effective is clinical audit as a tool where adverse outcomes are underreported or not reported?

See earlier comments on the term 'adverse events'.

NHSI does not have a direct role in relation to the commissioning and use of clinical audit to detect adverse outcomes, although it is supportive of work by partner organisations, and would anticipate evidence in relation to this question will be provided by NHS England.

6. What is the process by which patient safety incidents are collated and processed, and how are decisions made on issuing guidance as a result of these, either through the Central Alerting System, or by other means?

Please see the evidence provided above and the response to questions 4. and 5. and the attachments, especially Attachment D Patient Safety Review and Response Report which contains detail on this, and Attachments E & F examples of NHS Improvement Patient Safety Alerts. NHS Improvement Patient Safety Alerts are disseminated via the Central Alerting System

7. *Are regulatory decisions made with reference to the data capture of any/ all existing UK registries? If not, why not? Do any of the registries currently in operation meet the standards set by the International Medical Device Regulators Forum. Please highlight those that do. For those that do not are you able to say what are the common missing elements?*

This question is not within the remit of NHS Improvement; we do not commission or use registries

8. *Have you provided education and training programmes, and opportunities to share best practice for your members in the areas in the scope of the Review?*

NHS Improvement is not a provider or commissioner of clinical training or education, but it is supportive of work by partner organisations.

9. *Part of the remit of the Review is to make recommendations for the future management of these interventions. We would welcome your input on how to establish and accredit centres for excellence.*

NHS Improvement is not a provider or commissioner of accredited centres, but it is supportive of work by partner organisations.

10. *Part of the Review's remit is to consider wider systems of redress, and we would appreciate any input on the role of insurance and/or other redress mechanisms.*

NHS Improvement's remit does not cover processes for redress in response to adverse effects of drugs or devices or patient safety incidents. Colleagues in NHS Resolution would be well placed to advise further.

Please explain the basis for the evidence you are submitting to the Review, how that evidence was selected, the extent to which any relevant material has been withheld and the reasons why.

We have endeavoured to select the information that is most helpful to the Review, attaching more detailed documents where this may be helpful. We have not supplied information when we know this should be provided by partner organisations or would already be held by the Independent Review (e.g. we have not provided information on meetings we attended but which were hosted and organised by NHS England or MHRA, or copies of relevant parliamentary correspondence). We would be happy to provide more detail or more information once the Review has considered the above.

Other Information

We note the Independent Review directed this question at NHS England *"Do drug adverse events fall under the Serious Incidents Framework? If not, what framework would cover this?"* [GMBNSK Q.7]

Strategic responsibility for the Serious Incident Framework shifted to NHSI in April 2016 as part of the transfer of the Patient Safety Functions to NHS Improvement. While colleagues in NHS England may provide a response to this query, we thought it would be helpful for the Review to be directed to the 2015 Serious Incident Framework which defines Serious Incidents in NHS healthcare (Attachment C).

As noted in the Framework, the definition of a Serious Incident is not a black and white issue and the decision to declare a Serious Incident is usually a matter of judgement for the organisation in question. It is therefore possible that drug adverse effects could be declared a Serious Incident should there be reason to do so – for example where it is felt that the potential for learning is great enough to justify the investment required to undertake a full investigation. However, it is equally likely that many drug adverse effects would not be declared a Serious Incident and would simply be recorded via the Yellow Card system. Essentially it depends on the specific circumstances of the drug adverse effect in question.

We note the Independent Review directed this question at NHS England *"Looking to the future, what developments do you foresee in relation to adverse event monitoring and action?* [GMBNSK Q.17a]

As noted, strategic responsibility for the Serious Incident Framework shifted to NHSI in April 2016 therefore it is worth noting that the 2015 Serious Incident Framework is being reviewed following an extensive engagement exercise over this summer (2018). NHS Improvement intend to publish a revised Serious Incident Framework by April 2019 with a view to supporting improved learning and better engagement of patients and their families in the process of investigation. The information in relation to PSIMS and Yellow Card reporting above is also relevant to this question.

Please detail any commercial, financial or legal connection or interest in the pharmaceutical and medical devices industry sector (including subsidiaries) or any other body or organisation of interest to the Review.

None.

I hope this information is helpful. Please let me know if there is any additional information that you require.

Dr Aidan Fowler
National Director of Patient Safety
NHS Improvement

Attachments

- **Attachment A: National Patient Safety Incident Reports: Commentary (September 2018)**
  https://improvement.nhs.uk/documents/3266/NAPSIR_commentary_FINAL_data_to_March_2018.pdf

- **Attachment B: Patient Safety Alert: Resources to support the safety of girls and women who are being treated with valproate (6 April 2017)**
  https://improvement.nhs.uk/documents/911/Patient_Safety_Alert_-_Resources_to_support_safe_use_of_valproate.pdf

- **Attachment C: NHS England Serious Incident Framework (March 2015)**
  https://improvement.nhs.uk/documents/920/serious-incidnt-framwrk.pdf

- **Attachment D: Patient Safety Review and Response Report. October 2017 to March 2018 (25 September 2018)**
  https://improvement.nhs.uk/documents/3244/Review_and_Response_Report_Oct_2017_-_March_2018_v2.pdf

- **Attachment E and F: Example Patient Safety Alerts**
  - Patient Safety Alert: Resources to support safe and timely management of hypkalaemia (high level potassium in the blood) (8 August 2018)
    https://improvement.nhs.uk/documents/3121/Patient_Safety_Alert_-_Resources_to_support_safe_management_of_hyperkalaemia.pdf
  - Patient Safety Alert: Risk of death or severe harm from inadvertent intravenous administration of solid organ perfusion fluids (17 April 2018)
    https://improvement.nhs.uk/documents/2705/Patient_Safety_Alert_-_solid_organ_perfusion_fluids.pdf

The Independent Medicines and Medical Devices Safety Review

NHS Resolution's Submission

COI

NHS Resolution does not have any interests in the pharmaceutical or medical devices industries or similar. NHS Resolution does indemnify NHS trusts (and other NHS bodies) in England, and this may include NHS bodies against which claims have been made concerning sodium valproate and vaginal mesh.

NHS Resolution has also provided the Review Team with a copy of their Conflict of Interests Policy.

We address separately the three topics under consideration by the review.

1) Hormone Pregnancy Tests including Primodos

To the best of our knowledge we have never received a claim involving Primodos or other similar tests. Such tests are not usually undertaken by the members of our schemes, but rather by GPs or women themselves.

2) Sodium Valproate

Summary of NHS Resolution's involvement

In the late 1990s NHS Resolution (then known as NHS Litigation Authority) faced a growing group of claims brought by a disparate group of women/children who alleged that maternal ingestion of Sodium Valproate (SV) to treat the mother's epilepsy had resulted in damage to the fetus in utero. The women claimed that they had not been warned of the teratogenic effects of SV or given information regarding potential alternative anticonvulsants. Most of the claimants were publicly funded and in some cases, proceedings had been issued. At that stage, there was no co-ordinating group on behalf of claimants and they had a number of different solicitors representing them.

Eventually, NHS Resolution had 111 claims registered under a group code. One of our panel lawyers was instructed to investigate, advise and defend them. The claims had a potential for very high value.

During the course of investigating the claims we discovered that since the mid 1970's concern had been expressed about possible teratogenicity associated with anti-convulsant drugs generally, which were all considered to be teratogenic to a greater or lesser degree. SV was considered to be one of the better drugs compared with older anti convulsants. The British National Formulary (BNF) warnings applied to all anti-epileptic medications, not just SV. The risks associated with in utero exposure to anti-epileptic drugs were much more poorly defined than they are now.

There was no “ideal” drug for women considering pregnancy. Seizures pose a significant risk to health and in certain circumstances can even cause death. In pregnant women, they also pose a serious risk to the unborn baby, including intracranial haemorrhage and heart rate abnormalities potentially leading to permanent and irreversible brain damage.

SV was one of the most commonly used anti-epileptic medicines in the UK and was routinely prescribed to women of childbearing age. At the time we were carrying out investigations into the claims we were advised that at the point at which many of the women were prescribed SV, it was not widely known that it should not be used as a first line treatment in women of childbearing age.

As part of the investigations we met and took witness statements from a large number of treating clinicians who were responsible for prescribing SV to epileptic women. Many of them were neurologists working in trusts around the country, some were general physicians and some were GPs. A typical scenario we encountered was that a woman had been diagnosed with epilepsy, often during adolescence. The objective was to achieve good seizure control, preferably using only one anti-convulsant drug (“monotherapy”), and then to calibrate the dose to the lowest possible that maintained good seizure control. Once stability had been reached, women were often discharged back to the care of their GPs for long term follow up and the prescription of anti convulsants including SV continued in the community setting. Women taking SV often then presented to their GP or to ante natal clinics once they were already pregnant, often toward the end of the first trimester and sometimes beyond. At that point, the need to ensure effective seizure control was paramount for the safety of mother and baby. Monotherapy (as opposed to polytherapy) was preferable where possible which meant that clinicians were very wary of changing to an alternative drug as it is not possible to switch quickly from one anti convulsant to another. There has to be a period of weaning off and weaning on which inevitably involves a period of polytherapy.

As outlined above, some concern had been raised about possible teratogenic effects of anticonvulsant medications since the mid 1970s and historically clinicians who were treating female epilepsy sufferers who wished to start a family would probably have referred to the BNF for prescribing advice. It is clear that the advice available to clinicians evolved over time as the teratogenic properties of anticonvulsant medications became better understood and there was a wider appreciation of the nature and extent of the congenital abnormalities with which those medications were associated.

In 1981 the BNF (No.1) referred to then current anti-epileptics including Phenytoin, Carbamazepine, Primidone, Sodium Valproate, Ethosuximide and Clonazepam. There was a specific note on pregnancy:

> *“Pregnancy: although several anti-epileptics are teratogenic in animals the increased risk of congenital malformation in practice is slight. Abrupt withdrawal of anti-epileptics also carries risks of increased seizure frequency or status epilepticus*.”

Sodium Valproate was at that time the drug of first choice in the treatment of some epilepsies.

In 1984, the BNF advised that an increased risk of neural tube defects had been

reported but said that the reports were not substantiated. The BNF (No. 7) under "Anti-epileptics" continued to state that *"the benefit of treatment outweighs risk to the fetus."*

By 1986 the BNF (No. 11) advised as follows:

> *"PREGNANCY: during pregnancy, plasma concentrations of anti-epileptics should be frequently monitored as they fall particularly in later stages. There is an increased risk of teratogenicity associated with the use of anti-convulsant drugs, but this is in practice slight and, generally speaking, prescribing in pregnancy should follow the same principles as that in non-pregnant patients*".

In 1988 The BNF (No. 16) under the heading "Prescribing in Pregnancy, for anti-epileptics, said:

> *"The benefit of treatment outweighs the risk to the fetus; for further comments see section 4.8".*

In 1990/1991 the ABPI Datasheet Compendium, Sanofi on Epilim advised as follows:

> *"An increased incidence of congenital abnormalities in offspring born to mothers with epilepsy both untreated and treated has been demonstrated. There have been reports of fetal anomalies including neural tube defects in women receiving Valproate during the first trimester. This incidence has been estimated to be in the region of 1%. Such pregnancies should be carefully screened by alpha-fetoprotein measure and ultrasound and, if indicated, amniocentesis. In all pregnancies monotherapy is to be recommended and the benefits of anti-epileptic review must be evaluated against the possible risks and patients should be informed of these and the need for screening."*

By the mid 1990s, advice had begun to evolve. In 1995/1996, the ABPI Datasheet Compendium, Parke-Davies, though looking specifically at Epanutin, considered anti-convulsant medications more widely:-

> *"There were intrinsic methodological problems in obtaining adequate data on drug teratogenicity in humans. Genetic factors or the epileptic condition itself may be more important than drug therapy leading to birth defects. The great majority of mothers on anti-convulsant medication deliver normal infants. It is important to note that anti-convulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus. Anti-convulsants including Phenytoin may produce congenital abnormalities in the offspring of a small number of epileptic patients. The exact role of drug therapy in these abnormalities is unclear and genetics factors, in some studies, have also been shown to be important……"*

Guidance to professionals continued to stress the importance of controlling maternal epilepsy given the known adverse effects, particularly of status epilepticus, on the fetus.

In 1996 the ABPI Datasheet Compendium, Faulding Pharmaceuticals Plc, for Phenytoin injections, said:-

> *"Adverse affects on the fetus of status epileptcus, specifically hypoxia, make it imperative to control the condition. However, Phenytoin readily crosses the placenta and about 10% of exposed fetuses have been noted to show minor cranio-facial and digital abnormalities – the so called fetal hydantoin syndrome. Common features include broad lower nasal bridge, epicanthic folds, hypertelorism, malformed ears, wide mouth and hypoplasia of the distal phalanges and nails. A few of these babies have microencephaly and are retarded. Facial clefts and congenital heart disease are also seen more commonly than might be expected. Overall, however, the risk of having an abnormal child as a result of medication is far outweighed by the danger to the mother and fetus of uncontrolled epilepsy. The adverse effects on the fetus of status epilepticus, specifically hypoxia, make it imperative to control the condition in the shortest possible time…."*

Best Practice Guidelines for Women with Epilepsy (Seizure 1999) stated *"Women should enter pregnancy having complete seizure control or as few seizures as possible*". Clinicians tried to balance the risks of achieving good seizure control with the lowest therapeutic dose of SV possible on the basis that uncontrolled seizures are at least as dangerous to the unborn fetus, particularly Status Epilepticus.

Each of the individual claims would have been dependent on their own facts but following the investigations we undertook, we were confident that many of the claims brought were capable of being defended.

Part of our investigations involved consideration of whether the claimants had better prospects of success against the drug manufacturers, Sanofi Synthelabo. We obtained an advice from a QC who advised that he believed they did.

In 2003 we organised a meeting with the claimants' legal representatives, their leading and junior counsel and with the Legal Services Commission (LSC), as they were then known, also in attendance as public money was at stake on both sides. We explained the basis of why we believed the claimants had a better route against the manufacturers and handed over a copy of our QC's advice on a without prejudice basis. This set out the problems that the claimants would have to overcome in respect of causation if they pursued clinical negligence claims and set out the basis for how "defect" could be made out as regards the manufacturers.

After about a year, in 2004, we were told that the LSC had converted the certificates to pursue product liability claims and the claimants' legal representatives issued proceedings and a Group Litigation Order was made. We kept a close eye on the Fetal Anti Convulsant Syndrome (FACS) Litigation Register and this had 101 names on it. We closed our files.

We understand that the argument the claimants' legal representatives chose to plead was not exactly as per the advice from our QC but a modified format. Much later on, in about 2010, we were told by the claimants' legal representatives that the LSC had withdrawn funding for the product liability trial against the manufacturers just 3 weeks before it was due to commence leaving many of the claimants upset and feeling very let down.

The following analysis of the SV Claims statistics illustrates that the majority of the claims were notified to us between 1998 and 2002. More recently, we have started to

see a small trickle of newly reported claims. Again, following investigation, some of these more recent claims appear to be capable of being defended. We have settled 6 claims in total.

Response to Questions:

1. **Please could you provide the review with a fully anonymised summary of claims (number of claims, date of claims, outcomes) for each intervention**

   Please see below:

Sodium Valproate Statistics

Number of Claims	Year of Notification of Claim	Range of birth years	Status of Claims
1	1994	1989	Closed – Nil Damages
8	1995	1979-1993	Closed – Nil Damages
7	1996	1987-1993	Closed – Nil Damages
8	1997	1989-1995	Closed – Nil Damages – 7 Settled Damages Paid - 1
16	1998	1980-1997	Closed – Nil Damages
9	1999	1978-1996	Closed – Nil Damages
22	2000	1983-1999	Closed – Nil Damages
11	2001	1982-1998	Closed – Nil Damages
14	2002	1982-1997	Closed – Nil Damages – 13 Settled Damages Paid - 1
2	2003	1995-1998	Closed – Nil Damages
2	2004	2000-2002	Closed – Nil Damages
8	2005	1975-2004	Closed – Nil Damages – 7 Settled Damages Paid - 1
1	2006	1990	Settled Damages Paid
1	2007	1986	Closed – Nil Damages
1	2011	2001	Ongoing
1	2012	2009	Settled Damages Paid
1	2014	2009	Ongoing
2	2015	N/A (pregnancy terminated)	Ongoing – 1 Settled Damages Paid - 1
3	2018	1997-2012	Ongoing
Total Claims = 118			Total Damages Paid: £4,293,264 – 6 claims settled

2. a. **Please detail any insights you have developed from any mesh litigation that could be used to reduce the risk of, and costs associated with, future harm.**

   Not applicable to sodium valproate section.

b. **Please illustrate how upstream support close to the incident could be used to help resolve patient concerns for any of the interventions relevant to the Scope of the Review**

Much will depend on the definition of "incident" and whether this relates to the initial prescription of SV or the diagnosis, in a child born to a woman treated with sodium valproate, of some congenital abnormality or other problem associated with teratogenicity. The treatment of epilepsy in women of childbearing age has moved on considerably and a new regulatory position has been developed through close collaboration with professional bodies, health system organisations, and patient and campaign groups. Treatment is now informed by the NICE Pathway which is regularly reviewed and updated. The Pathway offers support and guidance to women and girls with epilepsy and is interactive and designed to be used online. The MHRA Patient Guide "What women and girls need to know about Valproate" is another source of support and signposts patients to various organisations and support groups. Clinicians now have a much deeper understanding of the risks associated with SV following the introduction of the Pregnancy Prevention Programme and the requirement for both specialist and patient to sign the Risk Acknowledgement Form ensures that patients are fully informed of the risks and available options. We have no further comments to make in relation to "upstream support" at the time of prescription of SV in light of the various initiatives which have been introduced relatively recently.

If the incident is when it is confirmed that a child has been damaged as a result of maternal ingestion of SV, then that could be many years following the initial prescription and quite possibly a considerable time following the birth, as conditions involving cognitive deficits but no obvious physical problem will not manifest until the child begins to miss key developmental milestones. Support at that time would involve prompt referral for multi-disciplinary review and treatment, with appropriate signposting to support groups and similar organisations. To the extent that it is envisaged that a compensation scheme is to be set up, appropriate and seamless referral would doubtless also be welcomed by affected families.

3. **How do you feel the culture of reporting concerns and adverse events by clinicians and others within the healthcare system has changed? What barriers, if any, do you feel inhibit open disclosure and reporting? What, if anything, could be done to improve this?**

The culture of reporting concerns and adverse events by clinicians and others within the healthcare system has been fundamentally overhauled following the introduction of the statutory duty of candour in November 2014.

Patients are now told if they have been affected by something which has gone wrong, they are provided with an apology and informed of the actions which have been, or will be, taken to prevent a recurrence. The introduction of this statutory duty has encouraged a culture of candour, openness and honesty. Our perception is that there has been a move away from a blame culture towards a more open culture in the NHS, where mistakes are more readily admitted, reported and discussed without fear of reprisal. That is not to say that that there are no longer any barriers which inhibit open disclosure and reporting. There will always be individuals who are reluctant to own up to mistakes or highlight areas of concern but this can be mitigated to some extent by effective leadership, an

acceptance of challenge and debate within the clinical setting and a culture of openness and transparency.

3) Synthetic Mesh – abdominal and vaginal pelvic mesh procedures

1. **Please could you provide the review with a fully anonymised summary of claims (number of claims, date of claims, outcomes) for each intervention.**

We sent a spreadsheet to Sir Cyril Chantler on 5th November.

The following grid summarises the position as at 30 September 2018:

Group 204 is the general code for these claims.

Group 212 is a special code for claims associated with a specific clinician in the W. Midlands.

	Group 204	**Group 212**
Total number of claims received	160	36
Closed (Nil Damages)	55	6
Settled	34	4
On-going claims/litigation	71	26
Damages paid (incl. interim payments)	£1,333,286	£327,798

2. Part of the remit of the Review is to make recommendations on how the healthcare System can improve its response when concerns have been raised about particular clinical interventions. We would welcome any input, with particular reference to the below:

a. Please detail any insights you have developed from any mesh litigation that could be used to reduce the risk of, and costs associated with, future harm

The vaginal mesh litigation has broadly been pursued across three main strands:

i. Consenting issues
ii. Unnecessary surgery and/or substandard surgical performance/follow up
iii. Product issues (directed to the manufacturers)

We are not in a position to comment on product issues so will respond with reference to (i) and (ii) only.

Consent

This is the main theme across the claims we are handling.

The allegations raised are that clinicians were not warning patients about the risks associated with the use of mesh/TVT implants. However, information relating to risks has increased and developed throughout the years. In some cases claimants are alleging that a clinician should have known about a particular risk associated with these implants but that risk may not have been a recognised complication at the time of the consent. For example, the risk of chronic pain was not included in the NICE/BSUG/RCOG Guidelines in 2013 but we are seeing claims relating to incidents occurring in or prior to 2013 where the allegation of failure to warn of this risk is being raised.

Allegations relating to inadequate consent are not specific to vaginal mesh claims but handling a large number has helped us to identify common themes. One such issue is sparsity and/or poor quality of records relating to discussions with the patients prior to surgery. This is especially prevalent in older cases where the surgery was five or more years ago. Where there is poor record-keeping, we face a factual dispute which means that the outcome of any trial is difficult to predict.

However, more recently the consent process has improved on the whole with more detailed and standardised consent forms, often completed and signed some time prior to the procedure, allowing the patient a period of reflection and consideration.

The introduction of information leaflets by many Trusts provides a safeguard for patients. Many Trusts adopt the BSUG/NICE/RCOG guidance. However, there is scope for leaflets to become more standardised and written in simpler terms. Perhaps women who have experienced the symptoms and have undergone surgery should be consulted to assist in the development of these leaflets.

Unnecessary and/or substandard surgery and/or substandard follow-up care

Allegations relating to substandard surgical performance do not tend to have a theme common to vaginal mesh surgery and are not being handled differently to any other claim alleging surgical error.

Allegations usually relate to inappropriate tape placement and/or inappropriate tension (i.e. tape too tight). Allegations relating to substandard follow-up care tend to concentrate on the failure and/or delay in diagnosis of post-operative complications (e.g. infection associated with the implanted device) or the failure to appreciate that the cause of the problems was related to the mesh which, on the Claimant's case, required removal.

The introduction of more/better training for clinicians who perform these procedures could address the issues and reduce the risk of future harm. This has already been addressed by the NICE guidelines which are due to be updated in the near future. We also welcome the recommendations made by Baroness Cumberlege to optimise care for women undergoing treatment for stress urinary incontinence and pelvic organ prolapse.

Many of the issues/concerns we see in the claims have already been, or are being, addressed. In addition to the Baroness' recommendations we suggest the following:

- Better record keeping including more detailed consent forms and information leaflets;
- Early involvement of physiotherapists and clinical nurse specialists to trial conservative treatments;
- Greater emphasis on alternative choices rather than offering only the 'gold standard' – this has more than likely improved following the *Montgomery* judgment
- Improved awareness of the potential complications (both for GPs and hospital clinicians) and early intervention when/if they arise
- Specialist tertiary centres taking complex referrals, mesh removal or excision surgeries

b. Please illustrate how upstream support close to the incident could be used to help resolve patient concerns for any of the interventions relevant to the Scope of the Review.

Patients undergoing vaginal mesh surgery span all ages. We have seen claims from women in their early 20's through to their 80's with the majority being in the range 35-55.

The main indication for surgery arises from childbirth, but that is not exclusively so. We do not have sufficient evidence to draw any distinction in symptoms between women who have had multiple births, birth complications including perineal tears, episiotomies, raised BMI, or those who have received post-natal pelvic floor physiotherapy. These are, potentially, areas for further investigation and for consideration to be given much earlier to what interventions could avoid the ultimate need for surgery for prolapse/incontinence.

The patient groups (through social media campaigning and in the course of litigation) have raised concerns that not enough was done by clinicians when complications arose. We see a high number of patients reporting that they felt they were not being listened to/believed, and a perception that complications were psychological in nature.

Many, although not all, patients now bringing claims did not report experiencing complications until many years after their surgery and therefore it is difficult to level criticism at the surgeons who were unable immediately to make a link. Many patients had comorbidities (prolapse and incontinence, chronic pain issues, orthopaedic complaints etc.) further complicating the diagnostic assessment.

In those cases where there is a prolonged time lag between surgery and the reported complication(s) it is difficult to see how any support closer to the 'incident' could or would have been of assistance. If the 'incident' is taken from the date the patient starts to report complications, this might be alleviated to an extent by considering the following issues:

- Fast-track referral from GP to tertiary centres offering tape excision/removal surgery, thus bypassing the Trust where the initial surgery took place – this could however have implications for NHS funding and resources.

- There are only a very small number of tertiary centres offering tape excision/removal surgery and the waiting lists are very long. We know some patients are paying for the treatment privately and even turning to crowd-funding and other sources to fund the treatment. It is clear from the mesh affected groups that shorter waiting lists and specialist intervention as soon as possible would be well-received. Again these would be dependent on NHS resources.

- There are concerns by patient groups that even now clinicians do not fully recognise (or accept) the risks associated with mesh surgery. It is hoped that with the implementation of new NICE guidelines and Baroness Cumberlege's recommendations, the issues surrounding mesh/TVT complications and problems will be at the forefront of clinicians' minds. The collection of data relating to the use of mesh should not only assist the NHS to identify those patient groups which are more at risk of developing prolapse/incontinence but also raise awareness of the incidence and type of complications arising so that earlier interventions can be implemented.

  A greater degree of dialogue with the campaign groups may assist to address concerns. However, this suggestion must be approached with caution because it is clear that patient groups do not want anything short of a total ban and that could be to the detriment of other patients who require mesh/TVT surgery to improve their quality of life.

3. How do you feel the culture of reporting concerns and adverse events by clinicians and others within the healthcare system has changed? What barriers, if any, do you feel inhibit open disclosure and reporting? What, if anything, could be done to improve this?

This is difficult to respond to, partially due to the fact that cultures vary from Trust to Trust and also between individual clinicians.

During our investigation of this group of claims we have not come across any trends or culture of not reporting adverse events or taking responsibility where appropriate. We have encountered clinicians/surgeons who readily accepted that alternative treatments were not discussed because they believed these would not relieve their patients' symptoms and mesh surgeries were considered to be the "Gold Standard".

It is likely that following the *Montgomery* judgment clinicians will reflect on those issues and apply the lessons learned to their current practice.

The introduction of the Duty of Candour provides a safeguard for clinicians and patients alike. We are not aware from our handling of the mesh claims that there is any problem in this regard in relation to mesh surgery.

It is likely that press coverage and increased awareness of mesh issues have improved overall disclosure and reporting.

National Institute for Health and Care Excellence

COI:

Declarations of interest for the Independent Medicines and Medical Devices Safety Review

NICE operates hospitality and declaration of interest policies which are regularly updated and through which we proactively seek declarations of interests which are held by staff, board members or advisory committee members, and any hospitality received from the life sciences industry. Declared interests are published on our website.

- The relevant policies can all be found on our policies and procedures page here: https://www.nice.org.uk/about/who-we-are/policies-and-procedures

- Declarations of interest for our Board and Senior Management Team can be found here: https://www.nice.org.uk/Media/Default/About/Who-we-are/Board/board-and-SMT-interests-register-2018-19.pdf

- Declaration of interest for other senior managers can be found here: https://www.nice.org.uk/Media/Default/About/Who-we-are/Board/senior-managers-interests-register.pdf

We also offer fee-paid services to the life sciences industry on a cost-recovery basis. This includes pharmaceutical, medical device and diagnostics companies. These programmes are separate from our guidance-producing activities.

Independent Medicines and Medical Devices Safety Review

NICE response to call for evidence

The National Institute for Health and Care Excellence (NICE) welcomes the opportunity to submit evidence to the Independent Medicines and Medical Devices Safety Review.

We have divided our response into general comments in order to provide information that we consider may be relevant to the work of your review and specific responses to the 14 questions posed in your letter.

General Comments

1. Since 1999, NICE has provided the NHS, and those who rely on it for their care, with an increasing range of advice on effective, good value healthcare. Improving outcomes for people using the NHS is a priority for NICE and this is underpinned by the guidance we produce; our guidance is informed by a rigorous, objective and independent assessment of the evidence. Across all NICE's work, we take particular care to capture the evidence of adverse effects of treatments. The interventional procedures programme, to which we refer extensively below, has a specific mandate to consider safety and efficacy of

procedures used for diagnosis or treatment that involves incision, puncture, entry into a body cavity, electromagnetic or acoustic energy.

2. In making recommendations we take full account of the fact that whilst no intervention can be entirely risk free, there will be patients with otherwise debilitating conditions who are able to benefit from such a procedure. We therefore aim to gauge the extent of uncertainties in the evidence and make recommendations on their implications for patients, clinicians and healthcare organisations, to ensure individuals can be supported to make decisions about their care which are right for them. The NHS has been instructed to make specific arrangements for use of interventional procedures in line with the Health Service Circular 2003/11[1]

3. Our guidance takes several forms:

- **Interventional procedures guidance** addresses the safety and efficacy of procedures for a specific indication and provides guidance on whether the procedures should be routinely used in the NHS, or whether any specific restrictions should be applied. Occasionally IP guidance will advise that a procedure should not be used in the NHS under any circumstances.
- **NICE guidelines** make evidence-based recommendations on a wide range of topics, including preventing and managing specific conditions, improving health and managing medicines in different settings.
- **Technology appraisals guidance** assess the clinical and cost effectiveness of health technologies, such as new pharmaceutical and biopharmaceutical products, but also include procedures, devices and diagnostic agents. This is to ensure that all NHS patients have equitable access to the most clinically - and cost-effective treatments that are viable. The NHS is legally obliged to fund and resource medicines and treatments recommended by NICE's technology appraisals.
- **Medical technologies and diagnostics guidance** help to ensure that the NHS is able to adopt clinically and cost effective technologies rapidly and consistently.

4. Independent committees develop the recommendations included in the output from all of these programmes. In case of the interventional procedures programme, the Interventional Procedure Advisory Committee (IPAC) advises NICE on the formulation of its guidance on the safety and efficacy of interventional procedures. The committee consists of health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. The committee takes advice from specialist advisors, nominated by health professional bodies whose members are involved in the use of interventional procedures.

5. Importantly, if a device is included in the interventional procedure that NICE is considering, the device must have a valid and current CE marking specific for the notified

[1] Health Service Circular 2003/11

indication before we produce the guidance. In the UK, all medical devices are subject to EU legislation, which use a CE marking to show compliance. Regulation of devices in the UK is a matter for the Medicines and Healthcare products Regulatory Agency (MHRA).

6. Senior staff from NICE and the MHRA meet quarterly to ensure a shared understanding and monitoring of key issues and activities to support a partnership agreement signed in July 2014 and updated in September 2018.

   Priority areas identified in the partnership agreement include:

- Development of guidance and advice
- Earlier access to medicines and healthcare products
- Transparency of clinical trial data
- Communication
- Research
- Innovation

Surgical mesh

7. NICE has produced recommendations that reference the use of synthetic mesh in the treatment of pelvic organ prolapse and stress urinary incontinence. Our work includes:

- Clinical guideline [CG171]: Urinary incontinence in women: management. Published date: This was first published in September 2013 and updated in November 2015. NICE is currently updating the recommendations on surgical approaches for stress urinary incontinence and has extended the scope to include pelvic organ prolapse. The updated guideline was published in draft for public consultation on 9 October 2018. The deadline for comments is 19 November 2018 and final guidance is expected to be published in April 2019.

- Interventional procedures guidance dealing with specific procedures using mesh to treat pelvic organ prolapse and stress urinary incontinence in women. These were published between 2005 and 2009 and were all updated over 2016-2017. A list of these is provided in Appendix A. During 2017 we developed new interventional procedure guidance on laparoscopic mesh pectopexy for apical prolapse of the uterus or vagina [IPG608]; published in March 2018.

8. The interventional procedures programme has also published guidance on procedures not for the treatment of pelvic organ prolapse or stress urinary incontinence where mesh is used; for example laparoscopic ventral mesh rectopexy for internal rectal prolapse [IPG618], published in June 2018. The programme is also currently developing guidance

on reinforcement of permanent stomas with mesh to prevent parastomal hernias; due for publication in April 2019.

Sodium valproate

9. With reference to your review of sodium valproate and other valproate medications for women of child bearing age, NICE has worked with the MHRA on this issue (as a member of the stakeholder group) since 2014.

10. NICE guidelines that refer to sodium valproate are:

- Epilepsies: diagnosis and management (CG137)
- Bipolar disorder: assessment and management (CG185)
- Antenatal and postnatal mental health (CG192).

11. Each guideline has been updated with links to the MHRA advice and a warning highlighting the pregnancy prevention plan on the guideline web page. A full update of the epilepsy guideline is underway (publication expected 2021).

12. NICE has disseminated the MHRA alerts and our response to these alerts through registered stakeholders, the NICE medicines and prescribing network, the NICE newsletters: 'Medicines awareness weekly', 'Medicines and prescribing: important new evidence', and 'Update for Primary Care' as well as NICE News and on Twitter/Facebook.

Responses to specific questions

1. ***Please could you provide a timeline outlining your understanding and recognition of risks regarding the interventions covered by this Review. This may include: initial recognition of the risk, dates of consequential and significant research studies, and communication of regulatory and professional guidance to clinicians and patients.***

Interventional procedures and recommendations related to mesh

13. In making recommendations we take full account the fact that no interventional procedure is entirely risk free, but that there may be patients with otherwise debilitating conditions who are able to benefit from such a procedure. This is reflected in the recommendations we make for patients, clinicians and healthcare organisations, to ensure individuals can be supported to make decisions about their care which are right for them.

14. We make 4 types of recommendations on interventional procedures:

- **Standard arrangements**
  - Use with standard arrangements for clinical governance, consent and audit.

- This is our most positive recommendation. It means that there is enough evidence for doctors to consider this procedure as an option. Doctors don't have to offer this procedure to patients and should always discuss the available options with the patient before making a decision[2]. You must also follow their hospital's policy about getting permission to perform operations and monitoring the results.

- **Special arrangements**
  - Use with special arrangements for clinical governance, consent and audit.
  - This recommendation means there are uncertainties about the procedure is safe and effective. We also recommend special arrangements if there are known risks of serious harm that need to be carefully explained to the patient before they make a decision. It emphasises the need for informed consent, both from the patient (or carer) and from senior medical staff, such as the clinical governance lead in their trust.
  - Clinicians using the procedure should also collect data, for example by audit or research. If there is no method of data collection already available for a procedure, we publish an audit tool alongside the guidance.

- **Use only in research**
  - This means that the procedure should only be carried out in the context of formal research studies, as approved by a research ethics committee.
  - We make this recommendation if the procedure is still considered to be experimental or because there are uncertainties that need to be resolved.

- **Do not use**
  - We make this recommendation if the evidence suggests that the procedure doesn't work well, or if there are unacceptable safety risks.

15. To give a specific example, the NICE guidance on posterior infracoccygeal sacropexy for vaginal vault prolapse (this is a mesh procedure), which was published in May 2005, specifically stated that:

- [1.1] Current evidence on the safety and efficacy of posterior infracoccygeal sacropexy for vaginal vault prolapse does not appear adequate for this procedure to be used without special arrangements for consent and for audit or research.
- [1.2] Clinicians wishing to undertake posterior infracoccygeal sacropexy should take the following actions.

[2] NICE – public involvement – your care

- Inform the clinical governance leads in their Trusts.
- Ensure that patients understand the uncertainty about the procedure's safety and efficacy and are fully informed of the alternative treatment options. Patients should be provided with clear written information and use of the Institute's Information for the public is recommended.
- Audit and review clinical outcomes of all patients having posterior infracoccygeal sacropexy for vaginal vault prolapse.

- [1.3] Further research will be useful and clinicians are encouraged to collect long-term data on clinical and quality-of-life outcomes. The Institute may review the procedure upon publication of further evidence.

16. Interventional procedures guidance indicating 'special' or 'research only' arrangements is reviewed after 3 years, and the guidance is updated if important new evidence is available. This may be done sooner if there is significant new evidence or emerging new safety concerns.

17. By 2009 the NICE interventional procedures programme had produced guidance on 7 procedures for the treatment of pelvic organ prolapse or stress urinary incontinence (Appendix A). Of these 5 of these had been given a 'special arrangements' recommendation, and one a 'research only' recommendation.

18. For the remaining procedure guideline (sacrocolpopexy using mesh for vaginal vault prolapse repair) the committee considered that the evidence on safety and efficacy of the procedure appeared adequate to support the use of this procedure provided that normal arrangements for clinical governance, consent and audit are in place. However, this was qualified in the recommendations by the following statements:

- Clinicians should ensure women understand that there is a risk of recurrence of vaginal vault prolapse after any prolapse-repair procedure, and that there is also a risk of complications, including mesh erosion (for example, into the vagina). They should provide women with clear written information. In addition, use of NICE's information for patients ('Understanding NICE guidance') is recommended.
- The procedure should only be carried out by surgeons specialising in the management of pelvic organ prolapse and female urinary incontinence.
- Evidence on safety and efficacy outcomes is limited to 5 years. Evidence on outcomes beyond 5 years and on the efficacy of different types of mesh would be useful. Further research should include patient-reported quality-of-life outcome measures using validated scales.

19. NICE was represented on the NHS England Mesh Working Group which published its interim findings in December 2015. We were therefore aware of the concerns which had been raised by patient groups and we were keen to actively contribute to the actions

taken by NHS England in order to assess the extent of any issues and what should be done to tackle them.

20. The 2015 interim report of the Mesh Working Group[3] made it clear that the MHRA had actively investigated reported issues with mesh implants used to treat pelvic organ prolapse and stress urinary incontinence with mesh manufacturers, professional clinical organisations and Notified Bodies[4]. The interim report further noted that the MHRA had also undertaken reviews of published research literature and that they had not found evidence to show that the pelvic organ prolapse and stress urinary incontinence mesh did not comply with the regulations.

21. In response to the concerns which had been raised, NICE decided to update all of its existing pieces of evidence based Interventional Procedures guidance relating to mesh used in the treatment of pelvic organ prolapse and stress urinary incontinence during 2016 and 2017 (Appendix B). NICE also decided to update its clinical guideline on urinary incontinence in women; extending the scope to include the treatment of pelvic organ prolapse. This is due for publication in April 2019.

22. The updated interventional procedures guidance on surgical procedures using mesh in the treatment of pelvic organ prolapse and stress urinary incontinence was based on the latest evidence available from the international peer reviewed literature; this was considered in the light of the concerns expressed by individual patients and patient groups.

23. The precise recommendation in each of the interventional procedures guidance was dependant on the nature of that evidence. Mesh related complications reported in the literature vary according to the procedure being considered. Evidence considered for safety and efficacy of the procedure is described in detail in the "overviews", published alongside NICE guidance, and this was taken into account by the committee when making their recommendation.

- For one (of the 7) Interventional Procedure Guidance documents that were updated, the recommendation became more restrictive moving from 'special arrangements' to 'research only' (transvaginal mesh repair of anterior or posterior vaginal wall prolapse).

- For another two the recommendation became less restrictive moving from 'special arrangements' to 'standard arrangements' for uterine suspension using mesh (including sacrohysteropexy) to repair uterine prolapse), and from 'only in research' to 'special arrangements' for single-incision short sling mesh insertion for stress urinary incontinence in women.

- For the remaining 4 the recommendation remained unchanged (3 'special arrangements' and one 'standard arrangements').

[3] NHS England Mesh Working Group
[4] MHRA Notified bodies for medical devices

24. The committee specifically used the update process to strengthen their comments about the precautions that were required when using mesh in procedures. The points made were as follows:

- There are serious and well-recognised complications of the procedure.
- Patient selection and treatment should only be done by specialists experienced in managing pelvic organ prolapse and urinary incontinence in women.
- Clinicians undertaking these procedures should have specific up-to-date training.
- The importance of patient consent – ensuring for example that patients understand the uncertainty about the procedure's safety, including the risk of mesh erosion.
- The importance of all adverse events involving the medical devices (including mesh) used in the procedure being reported to the Medicines and Healthcare products Regulatory Agency.
- The importance of data collection ideally through an appropriate registry.

25. Following the government's recommendation for a "pause" in the use of surgical mesh in July 2018 the following statement was placed on the NICE website page of all relevant interventional procedures guidance:

- *The Government has announced a pause on the use of vaginally inserted mesh and tape to treat stress urinary incontinence and pelvic organ prolapse in England. This follows a recommendation by Baroness Cumberlege, who is chairing an independent review of surgical mesh procedures and has heard from women and families affected by them. For details, see the letter from NHS England and NHS Improvement to trust medical directors. We will work with NHS England to produce a shared decision making tool, to be available when our updated guideline on guideline on urinary incontinence and pelvic organ prolapse publishes early next year.*

2. Please outline the process for recommending off-label use of drugs (for example the use of valproate medications for bipolar disorder). How frequently does this occur? Where does liability for adverse events lie, if a clinician is following NICE guidelines for off-label use

Use of off-label medicines

26. Recommendations in NICE guidance are usually about the use of medicines (often referred to as the licensed indications) for which the regulatory authority has granted a marketing authorisation, either in the UK or under the European centralised authorisation procedure. However, there are clinical situations in which the off-label use of a medicine may be judged by the prescriber to be in the best clinical interests of the patient. Off-label use may be recommended if the clinical need cannot be met by a licensed product and

there is sufficient evidence and/or experience of using the medicine to demonstrate its safety and efficacy to support this.

27. Off-label prescribing is particularly common in pregnant women and in children and young people (see below) because these groups have often been excluded from clinical trials during medicine development.

28. Comments are solicited from the relevant regulatory organisation; for example, the MHRA when the off-label use of medicines is likely to be considered within a guideline, or when advice is required on regulations related to medicines.

29. When prescribing a medicine off-label, the prescriber should follow relevant professional guidance (for example, the General Medical Council's Good practice in prescribing medicines – guidance for doctors[5]) and make a clinical judgement, taking full responsibility for the decision for the patient under his or her direct care. In addition, the patient (or those with authority to give consent on their behalf) should be made fully aware of these factors and provide informed consent, which should be documented by the prescriber. This is made clear in guidance whenever off-label use of a medicine is recommended.

NICE guideline on bipolar disorder: assessment and management

30. The example of use of valproate in the NICE guideline Bipolar disorder: assessment and management illustrates this approach. There are recommendations on its use, alongside recommendations on starting, monitoring, and stopping valproate. The guideline glossary explains what the term valproate refers to (the 3 formulations of valproate available in the UK: sodium valproate, valproic acid and semi-sodium valproate), and the complex licensing issues around this (at the time of publication only the semi-sodium valproate formulation had a UK marketing authorisation for the treatment of acute mania and for continuation treatment in people who have had mania that has responded to treatment with semi-sodium valproate. Both semi-sodium and sodium valproate are metabolised to valproic acid, which is the pharmacologically active component). This information is also contained in footnotes referenced when the term valproate is used within the guidance. The footnotes explain that sodium valproate is used commonly in UK practice, and explicitly state the responsibility of the prescriber.

31. At consultation stage of the bipolar guideline, 3 stakeholders commented that:

- *'The footnote that sodium valproate does not have marketing authorisation for some indications may confuse: perhaps the semisodium valproate part could be placed earlier so as not to possibly confuse people that valproate itself isn't licensed'*

32. NICE responded by reordering the footnote as suggested.

[5] GMC – good practice in prescribing and managing medicines and devices

3. **With specific regard to Levetiracetam, how have lessons learnt from valproate medications been applied to testing and guidance for newer anti-epileptic medications?**

33. It is not within NICE's remit to comment on this

4. **When will the next guidance on the management of stress urinary incontinence and pelvic organ prolapse be issued?**

34. The NICE guideline on Urinary incontinence (update) and pelvic organ prolapse in women: management is out for consultation. The anticipated publication date in April 2019.

35. In July 2018, the government accepted[6] a recommendation from the Independent Medicines and Medical Devices Safety Review to pause the use of vaginally inserted surgical mesh. The pause takes the form of a high vigilance restriction period. A notice about the pause was added to relevant published guidance on the NICE website. The draft guideline on urinary incontinence and pelvic organ prolapse in women which NICE is now seeking comments on from registered stakeholders consists of draft recommendations based on evidence reviews carried out by NICE between October 2017 and August 2018 and on the deliberations of an independent advisory committee.

36. Some of the draft recommendations propose a restricted place for vaginally inserted surgical mesh in the care pathways for both stress urinary incontinence and pelvic organ prolapse under certain circumstances. In consulting on these recommendations in the context of the pause, NICE is seeking stakeholder views on whether the recommendations in the draft guideline follow the evidence and are appropriate.

37. We are asking stakeholders to note that the publication of the final NICE guideline, which is due on 2nd April 2019, is just one of a number of conditions set out by NHS England and NHS Improvement in a letter to Acute Trust CEOs and medical directors about the pause. Until the conditions in the letter are met, the pause will remain in place. The other conditions are:

- Surgeons should only undertake operations for SUI if they are appropriately trained, and only if they undertake operations regularly.
- Surgeons report every procedure to a national database.
- A register of operations is maintained to ensure every procedure is notified and the woman identified who has undergone the surgery.
- Reporting of complications via MHRA is linked to the register.
- Identification and accreditation of specialist centres for SUI mesh procedures, for removal procedures and other aspects of care for those adversely affected by surgical mesh.

[6] Government announces strict rules for the use of vaginal mesh

5. **Please can you provide a brief summary of how adverse events reports are collected, processed and investigated? How effective do you think this process is in capturing adverse events data? How do you think this could be improved?**

38. Collection of adverse events related to the use of medicines or devices is the statutory responsibility of the MHRA. This is referred to as the "Yellow Card scheme"[7].

39. There are a number of ways of reporting to this system including on-line and through "Apps". It is generally accepted that adverse events are under reported through this system. This is also the case for any adverse event recording system elsewhere in the world. Any system which relies on voluntary reporting by individuals (patients or clinicians) will typically have significant under reporting.

40. In order to encourage reporting of adverse events NICE interventional procedures guidance for treatments of pelvic organ prolapse and stress urinary incontinence makes specific recommendations that all adverse events involving the medical devices (including mesh) used in that procedure should be reported to the MHRA.

41. NICE works closely with the MHRA and the MHRA's senior officer responsible for medical aspects of device regulation is a member of the Interventional Procedures Committee. If the MHRA gets reports of serious concerns about the safety of a procedure or device, it will notify the procedure to NICE which prompts an assessment by NICE or, if interventional procedures guidance has already been published, an update of this guidance.

6. **How do you facilitate signal detection by sharing information from international pharmacovigilance systems?**

42. When producing guidance on a procedure the interventional procedures programme routinely searches data from a number of sources. These are outlined in the programme manual. These will include for example the US Food and Drug Administration's Manufacturer and User Facility Device Experience (MAUDE) database.

7. **In your view, where within the healthcare and regulation system does your responsibility for disseminating and responding to adverse event reporting begin and end?**

43. NICE guidance is informed by a rigorous, objective and independent assessment of the evidence. Our guidance is widely consulted upon and made available both through our web site. Registered stakeholders are pro-actively notified about our guidance.

44. As mentioned above, NICE will routinely review any interventional procedures guidance given a 'special arrangement' or 'research only' recommendation every three years looking for any new evidence on safety or efficacy of that procedure. This may be done

[7] MHRA: Yellow Card Scheme: guidance for healthcare professionals

sooner if there is significant new evidence or emerging new safety concerns notified to NICE. Such notifications may come from any source including patients, clinicians, manufacturers or regulatory bodies.

45. In the event that the interventional procedures programme recommends that a procedure should "not be done" it specifically notifies the responsible NHS bodies in the 4 nations of the UK about that recommendation (in England this would be NHS Improvement).

46. NICE disseminates information about adverse event reports for medicines by:

- Publishing MHRA drug safety updates in a quarterly medicines evidence commentary, in conjunction with the MHRA. This is sent as part of NICE's medicines awareness service to around 11,500 subscribers.
- Highlighting medicines and patient safety alerts issued by MHRA and NHS improvement in a monthly digest of important new evidence in medicines optimisation. This is sent to around 2,700 subscribers.
- The NICE medicines team (compiling these summaries) assess the alerts and, if judged to be of high clinical importance and likely to change NICE recommendations, shares with relevant guidance team at NICE. The assessment criteria are attached below (response to Q8).
- Highlighting key medicines safety issues (such as the use of sodium valproate in girls and women) to a network of ~ 80 health professionals working in medicines optimisation (NICE medicines and prescribing associates) through contact training days. The network then disseminates these messages within their local health economies.
- Medicine evidence commentaries are short reviews of important new evidence relating to medicines and prescribing. When the medicines team at NICE assess new evidence for possible inclusion as a commentary, any safety issues are highlighted to relevant teams at NICE and to the MHRA if appropriate.

8. Please can you provide details of your relevant policies and protocols, if any, for ensuring that information relevant to patient safety, and learning from adverse events is disseminated.

Medicines awareness

47. NICE has a medicines awareness service to help health and social care professionals make better decisions. We work with medicines information specialists in the Special Pharmacy Service to provide rapid access to current awareness and evidence-based medicines information relevant to their area of interest or speciality, by providing links to published evidence, policies, guidelines, evidence evaluations and news.

48. Individuals can subscribe to daily (currently ~18,000 subscribers) or weekly digests of information (currently ~11,500 subscribers).

49. Attached as appendices to this response are the content strategy (Appendix C), standard operating procedure (daily) (Appendix D) and standard operating procedure (w) (Appendix E) for our medicines awareness service.

Medicines and prescribing associate network

50. The NICE Medicines and Prescribing Associates form a network of around 80 health professionals (covering each sustainability and transformation/integrated care partnership), working in medicines optimisation across England, Wales, Northern Ireland and the Channel Islands. The associate network includes pharmacists, GPs and nurses working in diverse settings across primary and secondary care, mental health, prison and defence services.

51. NICE supports their work by providing materials and training on new NICE guidance and national issues in medicines optimisation, through 5 contact training days each year. Patient safety topics covered include the MHRA yellow card scheme, sodium valproate in women and girls, inhaled corticosteroid use in asthma, and the national review of asthma deaths report. The associates then disseminate this information to their affiliate networks; local health and social care professionals with whom they share intelligence and support.

52. There are 4 NICE medicines implementation consultants who help associates build their local networks, and develop local links to facilitate dissemination of information between NICE, associates and regional organisations such as Regional medicines optimisation committees (RMOCs), RightCare delivery partners, Public Health England and Skills for Care.

Medicines vigilance

53. The medicines awareness alerts support medicines vigilance performed by the NICE medicines team. Alerts are scanned for information relevant to patient safety, using a topic selection and checklist to signpost people:

- Is any medicine that has been withdrawn or had a safety warning from the MHRA mentioned in NICE guidance/evidence summaries?
- Has any guidance from NHS England or Department of Health and Social Care relating to medicines use been published that impacts on NICE guidance/evidence summaries?
- Have any studies been published that might be suitable for a medicines evidence commentary?
- Have any studies been published that might be relevant to review of NICE guidance?

54. Evidence that is identified as likely to affect existing NICE guidance/advice is brought to the attention of the relevant Associate Director at NICE for further action.

55. Evidence selected for further discussion is recorded on a spreadsheet that supports a monthly review meeting, with the following possible outcomes:

- Information to be provided to relevant team at NICE
- Topic selected for production of an evidence commentary
- Topic not selected
- Dissemination of information from NICE, MHRA and NHS Improvement via:
  - monthly digest of important new evidence in medicines optimisation (currently ~ 2,700 subscribers)
  - quarterly medicines evidence commentary containing content from MHRA drug safety updates, included in medicines awareness weekly newsletter.
  - the NICE medicines and prescribing associate network as described above.

9. Are regulatory decisions made with reference to the data capture of any/ all existing EU registries? If not, why not? Do any of the registries currently in operation meet the standards set by the International Medical Device Regulators Forum. Please highlight those that do. For those that do not are you able to say what are the common missing elements?

56. NICE makes use of registers to collect data for technologies that require more evidence to inform future decision-making. This is particularly so for the Interventional Procedures Programme which may recommend the collection of further data in specific named registers, with the intention of enriching the evidence base for the technology in order to inform future reviews of the guidance.

57. The IP programme manual specifies four standards that should be met by any recommended register, namely:

- All known procedures (all devices), without exception, are recorded in the database.
- The data recorded address relevant efficacy and safety outcomes and important patient characteristics.
- There is independent oversight of the register.
- The register complies with the data protection principles laid out in the UK Data Protection Act 1998 and any other relevant legislation.

58. We have recently objectively reviewed the quality of the registers that we recommended and concluded that:

- Overall, the quality of registers recommended by NICE was disappointing, with a split between large registries that scored highly across all standards and smaller registries that scored poorly.

- Only a limited number of registers recommended by NICE are mature enough to deliver evidence of sufficiently high quality to inform funding decisions.

59. This work has been peer reviewed and published in the European Journal of Public Health.[8]

10. What factors influence the decision on when to update guidance, and how are adverse events reports weighted in this process given the known level of underreporting?

60. NICE will routinely review any interventional procedures guidance given a special arrangement or research only recommendation every three years looking for any new evidence on safety or efficacy of that procedure. This may be done sooner if there is significant new evidence or emerging new safety concerns notified to NICE. Such notifications may come from any source including patients, clinicians, manufacturers or regulatory bodies.

61. A decision on whether to update guidance is taken after consultation with specialist advisors (ratified by the relevant specialist society) and a review of the published literature and approval by NICE's Guidance Executive.

62. Assessment of safety is a key feature of the interventional procedures programme's methods. Therefore, studies that systematically report adverse events are sought. Safety outcomes are often not well addressed in randomised trials. Large numbers of treated patients are needed to reliably detect uncommon yet serious adverse events.

63. Large case series, surveys, registers and case reports may provide valuable information, for example, for procedures where there is concern about the potential for rare but serious complications. Although these sources lack data to support incidence calculations, they provide information that can be highly relevant. This is particularly the case for serious adverse events that occur with procedures used to treat conditions that have little impact on quality of life or with a good prognosis.

64. A process for linking MHRA Drug Safety Updates (Appendix F) helps to assess the significance of a safety alert from MHRA, and is used by the medicines team at NICE to inform the relevant guidance teams at NICE of any issues.

11. What evidence do you consider as part of your evidence-based guidance? Please list what sources you consider. If this evidence raises concerns, what actions do you take?

65. Data on efficacy of a procedure is only taken from the peer reviewed literature or appropriate registers. Data on safety, however immature, may come from abstracts, companies, registers, specialist advisers' reports and other miscellaneous sources. The

[8] European Journal of Public Health, Volume 28, Issue 2, 1 April 2018

programme team always brings such data to the IPAC's attention, regardless of source, when safety issues relating to serious adverse events are identified. Unpublished evidence is used when this shows safety outcomes that have not been reported in published sources.

66. When the evidence suggests that a procedure has no efficacy or poses unacceptable safety risks, the committee recommends that it should not be used.

67. If there needs to be resolution of substantial uncertainties about the efficacy or safety of a procedure the interventional procedures committee recommends controlled investigation of the procedure under the scrutiny and protection of research ethics committees (research only recommendation).

68. When there are significant uncertainties in the evidence on efficacy or safety, or an inadequate quantity of evidence or the balance of risks and benefits are unclear, the committee will recommend 'special arrangements'. The clinicians using the procedure must then inform the clinical governance lead in their trust, tell the patient about the uncertainties regarding the safety and efficacy of the procedure and collect further data by means of audit or research.

69. The NICE medicines team use medicines safety alerts from MHRA, and summaries of product characteristics when they quality assure new NICE guidance prior to publication. This involves a review of prescribing and medicines content, by a technical expert (pharmacist), and includes specific medicines safety and licensing questions:

- For the current medicines related recommendations, follow the NICE Drug safety alert process. (see Appendix F)
- For medicines identified through the surveillance review which are not currently included in the guideline highlight any MHRA drug safety updates that may affect the update decision e.g. if the medicine identified has been withdrawn or if a drug safety update says that the drug should only be used for a specific indication.
- Check that all medicines recommended in the guideline are either licensed for the indication/dose/route/population they are being recommended for or are appropriately footnoted as being off-label.

12. When changes are made to prescription licensing, who is responsible for compliance with the new regulations? How is this monitored?

70. It is not within NICE's remit to comment on this

13. Where does responsibility lie for monitoring the update of guidance for prescribing, and for ensuring compliance with regulations?

71. Surveillance of NICE guidelines includes a review of prescribing and medicines content, by a technical expert (pharmacist) within the NICE medicines team.

72. The checklist (Appendix G) includes specific medicines safety questions:

- For the current medicines related recommendations, follow the NICE Drug safety alert process. (see Appendix F)
- For medicines identified through the surveillance review which are not currently included in the guideline highlight any MHRA drug safety updates that may affect the update decision e.g. if the medicine identified has been withdrawn or if a drug safety update says that the drug should only be used for a specific indication.

73. NICE guidelines make authoritative, independent and evidence-based recommendations on a wide range of topics in health, public health and social care. We maintain that our recommendations about the use of new medicines, medical technologies and diagnostics identify the most clinically- and cost-effective treatments available. We work closely with local and national organisations including NHS England, the Care Quality Commission, Public Health England, NHS Improvement, and Health Education England. Together we encourage and support a quality- and safety-focused approach, in which commissioners and providers use NICE guidance and other NICE-accredited sources to improve outcomes.

74. Our guidance, advice and quality standards are made available in a variety of formats to ensure they are easily accessible to users through the NICE website.

75. Different types of NICE guidance have a different status within the NHS, public health and social care. Of particular relevance:

    a. Our technology appraisals and highly specialised technologies guidance are unique because the NHS in England and Wales is legally obliged to make available medicines and treatments recommended through our technology appraisal programme. The legal status of these programmes is reinforced in the NHS Constitution, which states that patients have the right to drugs and treatments that have been recommended by NICE for use in the NHS, if the doctor responsible for the patient's care says they are clinically appropriate.

    b. Our IP guidance is system advice on whether the procedures should be routinely used in the NHS, or whether any specific restrictions should be applied (see section 2 and 3 above).

76. None of our other guidance and products is subject to the same legal obligations as our technology appraisals and highly specialised technologies guidance. Nevertheless, health and social care professionals are actively encouraged to follow our recommendations to help them deliver the highest quality care. Our recommendations are not intended to replace the professional expertise and clinical judgement of health professionals, as they discuss treatment options with their patients and we recognise that there will be occasions where it would not be appropriate for an individual to be treated as NICE guidelines suggest. However we would consider it best practice that clinicians should take into account NICE guidelines in their decision making and in the event of a decision not to

follow them, this to have been discussed with the patient and documented in the clinical record.

77. Responsibility for the implementation of NICE guidance does not fall to any single body but requires a system wide approach. The arrangements for the UK wide application of guidance from the interventional procedures programme were previously outlined in the Health Service Circular (HSC) 2003/011 (The interventional procedures programme: working with the National Institute for Clinical Excellence to promote safe clinical innovation). Provider organisations' compliance with this HSC was assessed by the regulatory bodies (such as the Commission for Health Improvement) operating in the NHS at the time. However following the changes to NHS structures in the UK the HSC is no longer current. There is no requirement on the CQC, as successor to the Commission for Health Improvement, to ensure compliance with NICE's interventional procedure guidance.

78. NICE has therefore agreed an updated document[9] with the relevant NHS policymakers from the 4 Nations of the UK which is available on our website[10] (see 'Safely introduce new procedures into your practice'). The importance of this document has been highlighted by NHS Improvement to NHS providers in England.

79. This document lays out the responsibilities of NHS organisations and states that:

- All NHS providers of healthcare should ensure they have governance structures in place to review, authorise and monitor the introduction of new interventional procedures or the use of established clinical procedure, the efficacy or safety of which has been called into question by new information or advice.
- When the recommendation about a procedure from NICE includes collecting data on outcomes and safety, health care organisations should ensure systems are in place to support health care professionals to supply the information requested on every patient undergoing the procedure. The data on the outcomes and safety of that procedure should be reviewed by the organisation. The individual undertaking the procedure should also be expected to discuss their outcomes as part of their annual appraisal to allow reflection, learning, and individual improvement.

80. NICE believes there are opportunities for the system to encourage that its advice is being considered and used as intended. These could include:

- Oversight by the regulator (CQC or NHS Improvement) to provide assurance that providers of health care have governance structures in place to review, authorise and monitor the introduction of new interventional procedures in line with the recommendation from NICE.

[9] nice/using-new-IPs-requirements-NHS-and-clinicians
[10] nice /about/what-we-do/our-programmes/nice-interventional-procedures-guidance

- Using the trust appraisal system to ensure clinicians adhere to clinical guidance and comply with national data requirements and report complications. With respect to procedures using mesh the NHS England working party report recommended that a section of the appraisal should ask surgeons performing procedures using mesh if they are:
  - adhering robustly to NICE guidance (including informed consent, and advice on and means of recording any derogation from NICE guidance)
  - appropriately trained and current in their practice
  - reporting the procedure on a national database e.g. the BSUG database
  - reporting adverse incidents (AIs) to MHRA

81. These principles would apply equally well to clinicians undertaking any interventional procedure (not just those related to the use of mesh)

82. Clinicians should be required to explain any non-compliance and for taking action to address such non-compliance.

83. Where submission of data on a procedure to national registers is recommended systems should be put in place to support health care professionals to supply the information requested on every patient undergoing the procedure. It is essential that resources are also in place to ensure this data is of sufficiently high quality, analysed and published so that it can be used by health technology assessment agencies to produce and update guidance.

14. Does the fact something is a known teratogen affect pre- and postmarketing testing and guidance? In addition to inclusion of the information on the label, are other measures taken? Do you consider these measures to be sufficient?

84. It is not within NICE's remit to comment on this.

Appendix A

Interventional procedures guidance dealing with specific procedures using mesh to treat pelvic organ prolapse and stress urinary incontinence published between 2005 and 2009

IPG283 - Sacrocolpopexy using mesh for vaginal vault prolapse repair	Published March 2007: Standard arrangements Updated January 2009: Standard arrangements
IPG280 - Infracoccygeal sacropexy using mesh for uterine prolapse repair	Published January 2009: Special arrangements
IPG281 - Infracoccygeal sacropexy using mesh for vaginal vault prolapse repair	Published May 2005: Special arrangements Updated January 2009: Special arrangements
IPG282 - Insertion of mesh uterine suspension sling (including sacrohysteropexy) for uterine prolapse repair	Published January 2009: Special arrangements
IPG267 - Surgical repair of vaginal wall prolapse using mesh	Published June 2008: Special arrangements
IPG262 - Single-incision sub-urethral short tape insertion for stress urinary incontinence in women	Published May 2008: Only in research
IPG284 - Sacrocolpopexy with hysterectomy using mesh for uterine prolapse repair	Published January 2009: Special arrangements

Appendix B

All current NICE Interventional Procedures guidance relating to mesh used in the treatment of Pelvic Organ Prolapse (POP) and Stress Urinary Incontinence (SUI). All were updated and published in 2016-2017.

IPG number	Procedure Name	Publication Date	Recommendation
IPG583	Sacrocolpopexy using mesh to repair vaginal vault prolapse	Jun-17	Standard
IPG582	Infracoccygeal sacropexy using mesh to repair uterine prolapse	Jun-17	Special
IPG581	Infracoccygeal sacropexy using mesh to repair vaginal vault prolapse	Jun-17	Special
IPG584	Uterine suspension using mesh (including sacrohysteropexy) to repair uterine prolapse	Jun-17	Standard
IPG599	Transvaginal mesh repair of anterior or posterior vaginal wall prolapse	Dec-17	Only in research
IPG566	Single-incision short sling mesh insertion for stress urinary incontinence in women	Oct-16	Special
IPG577	Sacrocolpopexy with hysterectomy using mesh to repair uterine prolapse	Mar-17	Special

Appendix C

Medicines Awareness Services: Content Strategy

Medicines Awareness Daily and Medicines Awareness Weekly

Version no.	Date	Name	Summary of changes
1.0	10.11.2012	[redacted]	First draft
1.1	12.11.2013	[redacted]	Editing of first draft
1.2	15.11.2012	[redacted]	Editing of first draft
1.3	16.11.2012	[redacted]	Tracked changes accepted
1.4	21.11.2012	[redacted]	Update on access to journal articles abstract following discussion with UKMI [redacted]
1.5	07.01.2013	[redacted]	Consultation comments and changes collated from gIS, MPP, UKMI and [redacted]
2.0	17.01.2013	[redacted]	Alignment of information categories with display of content in MAD
2.1	18.01.2013	[redacted]	Agreed changes from V1.5 consultation comments with [redacted]; Addition of Appendix C and D.
2.2	22.01.2013	[redacted]	Comments and suggestions for change from eIS
2.3	04.02.2013	[redacted]	Update of information categories following consultation with eIS and Search, and related reordering of document content.
2.4	12.02.2013	[redacted]	Re-ordering of information categories; addition of specialty area appendix.
2.5	15.02.2013	[redacted]	Highlighting areas for MPP to review and input
2.6	26.02.2013	[redacted]	Comments and clarifications from telephone discussion with UKMI incorporated
2.7	01.03.2013	[redacted]	Comments and clarifications from MPP incorporated.
3 0	15.03.2013	[redacted]	Final consultation – incorporation of comments from [redacted], [redacted], [redacted] and UKMI from training sessions.
3.1	25.10.2013	[redacted]	Document review – small editorial changes; inclusion of guidance for excluding MAD content in the MAW agreed with MPP; change of information category 'Press and media' to Media and Commentaries
3.2	18.11.2013	[redacted]	Feedback from UKMI on v3.1; accepted v3.1 changes
3.3	09.02.2015	[redacted]	Document review and update, including source list in Appendix A; inclusion of syndication statement
3.4	12.05.2015	[redacted]	Addition of MPP responsibility to add NICE Guidance references to short summaries.
3.5	03.02.2016	[redacted]	Review of document and source list
3.6	10.05.2017	[redacted]	Remove references to Eyes on Evidence. Updated Types of Information to Evidence Types including mapping in Appendix C.
3.7	26.10.2017	[redacted]	Reviewed. Updated MPC to MPP. Added supplementary guidance notes on including NICE products (previously a separate document) as Appendix D.

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1. Introduction

From April 2013, NICE, working with the UK Medicines Information service (UKMI), took on responsibility for the delivery of the NICE medicines awareness service This awareness service, consisting of a daily and weekly option, replaced the NeLM daily newsletter and the NICE Medicines and Prescribing Programme (MPP) Medicines Awareness products (formerly e-CAB).

This service supports the aim of NICE and NICE Evidence Services to help empower health and social care professionals to make better decisions by providing rapid access to current awareness and evidence-based medicines information relevant to their area of interest or speciality, by providing links to published evidence, policies, guidelines, evidence evaluations and news.

This content strategy details the inclusion and exclusion criteria, content prioritisation and governance supporting the delivery of the daily and weekly medicines awareness service, to ensure it provides an informative and useful service for NICE and NICE Evidence Services users and subscribers.

2. Medicines Awareness Service

2.1. Audience

Although the service may also be of value to all 'My NICE' subscribers and users of all NICE services, the key intended audience groups are healthcare professionals whose practice involves commissioning, managing, prescribing, dispensing or administering medicines.

2.2. Service Elements

The medicines awareness service highlights the following types of information where these relate to medicines and prescribing:

- new guidance publications from key sources such as NICE and other accredited UK guidance producers.
- new and updated prescribing information to inform clinical practice including drug appraisals, evidence summaries and reviews.
- selected evidence published in major journals.
- news aggregated from news stories, press releases and safety alerts from agreed sources.

The service produces two complementary outputs. Subscribers are able to select whether they wish to receive the Medicines Awareness Daily and/or the Medicines Awareness Weekly service.

The **Medicines Awareness Daily** is primarily intended for health professionals for whom commissioning and managing the use of medicines are significant parts of their work, and ensuring that wider healthcare professionals are aware of important information relating to medicines and prescribing.

The **Medicines Awareness Weekly** is primarily intended for health professionals whose practice involves medicines, and for whom a selection of the week's most important information is sufficient.

2.2.1. Medicines Awareness Daily (MAD)

Content identified by UKMI is published at the end of each working day. This is sent to Medicines Awareness Daily subscribers as an email (subscribers can elect to have content limited to identified areas of interest via the Login>Preferences setting), with the content searchable in NICE Evidence Search on the same day, with relevant tagging and appropriate ranking. Approximately 15 - 20 records are featured each day.

2.2.2. Medicines Awareness Weekly (MAW)

UKMI is responsible for ranking each Medicines Awareness Daily record for potential inclusion in the Medicines Awareness Weekly. Each record is ranked 1-3, with 1 referring to records which are strongly recommended for inclusion in the Medicines Awareness Weekly and 3 to records not considered to be of sufficient importance to merit inclusion.

The Medicines Awareness Daily records are then reviewed and assessed by a MPP pharmacist editor for inclusion in the email that week to be sent to all subscribers of the Medicines Awareness Weekly. Not all records from the daily service can be included in the weekly service; content is restricted to approximately 30 records.

Additional reference to relevant NICE guidance (published and planned) is added to the record summary by MPP staff to be highlighted via the Medicines Awareness Weekly. (Due to the time involved in this activity, UKMI are only expected to add NICE guidance references to Medicines Awareness Daily record in relevant UKMI Comments).

The Medicines Awareness Weekly also contains an approved Medicines Evidence Commentary produced by NICE, see section 5.1 for more detail.

3. Inclusion criteria

3.1. Overarching criteria

The overarching criteria for the inclusion of content in the medicines awareness service are:

- Direct relevance to medicines and prescribing in its broadest context;
- Information that requires, or has the potential to require, a change in practice;
- Written in English with relevancy to UK practice and the UK Health System (if not from the UK the information must update UK practice and must be from a respected European Union/International source);
- Pertains to diseases and conditions relevant to UK clinical practice;
- Recently published new or updated content (usually within one month of publication);
- Open access to full text or abstract, either in the public domain or via NHS ATHENS authentication.

3.2. Relevance Assessment

Assessing relevance for content inclusion in the medicines awareness service can be judged according to six criteria:

- **Impact**: is this information likely to impact or challenge common practice in UK primary or secondary care?
- **Outcome**: for studies of interventions, is the outcome measured of direct relevance to patients/carers? That is, does it directly measure whether use of the intervention affects the quality or duration of their life? Please note: there may be some reliable surrogate outcomes, such as smoking cessation rates.
- **Incidence and Prevalence**: is the clinical condition or operational practice common in UK primary or secondary care? Is it in a key therapeutic area (top 40)?
- **Feasibility**: is implementation of the intervention in usual practice likely to be generally feasible?
- **Evidence:** is the type of evidence significant in terms of the evidence hierarchy and type of study.
- **Source:** Give weighting to accredited guidance producers and key sources. For example, NICE, SIGN, MHRA, DH, SMC.

3.3. Categories and criteria for the Medicines Awareness Daily

Sections 3.3.1 to 3.3.8 detail the overarching information categories and information types that fall within them, summarising the content areas included in the medicines awareness service. In addition:

- **Appendix A** lists the sources to be scanned daily.
- **Appendix B** provides definitions for each information type.
- **Appendix C** lists the mapping of the information types to the NICE Evidence Search Evidence Types filter.

3.3.1.GUIDANCE AND ADVICE

- **Guidance**
  Newly published or updated systematically developed statements to guide decisions about health and social care, from national organisations and selected accredited guidance producers specific to UK practice, for example, the National Institute for Health and Care Excellence and Scottish Intercollegiate Guidelines Network, and international sources with relevance to UK practice.

  See Appendix D for supplementary guidance notes on including NICE products.
- **Drug best practice guidance**
  Other newly published or updated guidance and recommendations to support the optimal

use of medicines from national organisations producers relevant to UK practice, including advice from the Scottish Medicines Consortium and All Wales Medicines Strategy Group.

- **Commissioning guides**
  Commissioning guides and resources to inform local NHS planning and decision-making, for example guides produced by the National Institute for Health and Care Excellence.

- **Drug prescribing**
  Technical information to support the safer prescribing of medicines, including British National Formulary drug monograph updates and significant product licence changes from the electronic Medicines Compendium.
  NB: Product licence changes may be identified from manufacturers but need to link to Summary of Product Characteristics listed by the electronic Medicines Compendium.

3.3.2.SAFETY ALERTS

Safety alerts and recalls content covering UK drug withdrawals, and patient safety and medical device alerts where relevant to medicines and prescribing, from the Medicines and Healthcare products Regulatory Agency.

Safety and alerting information from key international regulatory sources with a relevance to UK practice, for example, European Medicines Agency and US Food and Drug Administration.

3.3.3.SYSTEMATIC REVIEWS

Newly published or updated systematic reviews and health technology assessments relating to medicines and prescribing for conditions and diseases relevant to UK clinical practice.

NB: The Medicines Awareness Service should link to full text where freely available. For gated full text please link to abstract.

- **Systematic reviews**
  Systematic reviews/ meta-analysis of medicines or lifestyle interventions, for example, the Cochrane Database of Systematic Reviews and those published by a journal which conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard. Systematic reviews from other journals are deemed reliable if the abstract reports the inclusion/exclusion criteria, confirms two or more sources have been searched, and incorporates a synthesis of included studies.
  NB: Cochrane content is to be limited to systematic reviews with specific relevance to medicines awareness i.e. there is no longer a requirement to list all systematic reviews published by Cochrane.

- **Health technology assessments**
  Assessments determining the clinical and cost effectiveness of a health technology.

3.3.4.EVIDENCE SUMMARIES

- **Evidence summaries**
  Summaries of the best available evidence related to medicines and prescribing including clinical review articles, NIHR Signals and the MPP Evidence summaries: new medicines, and Evidence summaries: unlicensed/off-label medicines, both designed to meet demand for information to inform local NHS planning and decision-making.

- **Medicines evidence commentaries**
  A weekly publication from NICE MPP, providing information on new evidence on medicines currently in use for NHS commissioners, prescribers and prescribing managers. Only to be included in the Medicines Awareness Weekly. See section 5.1.

- **Medicines Q&A**
  UKMI produced evidence-based, quality assured answers to selected medicines-related enquires made to local medicines information services.

3.3.5.PRIMARY RESEARCH

To support evidence-based practice, content in these categories is to cover primary research into medicines (or lifestyle interventions involving medicines) relating to conditions and diseases relevant to UK clinical practice.

The three categories of primary research are:

- **Randomised controlled trials (RCTs)**
  Phase III RCTs relevant to medicines and prescribing, for example studies of new drugs, new studies of established drugs and post-marketing studies that improve knowledge about safety profile of established drugs.

  Phase II RCTs where:

  - the study sample is relatively large considering the disease/condition (smaller studies can be considered in rare diseases relevant to UK clinical practice);
  - the study investigates new drugs where the condition is not already successfully treated by a drug;

  NB: 'Uncontrolled Phase II studies may be considered for inclusion in exceptional circumstances'

- **Other primary research**
  Newly published or updated primary research which is not a RCT or ongoing or unpublished research, for example, observational, cohort, and case control studies.
  Post-hoc analyses of clinical trials are to only be included where regarding conditions and diseases relevant to UK clinical practice, and where the analysis adds important information.

- **Ongoing or unpublished research**
  Including horizon scanning trial information and conference abstracts.

To support this as awareness raising service, journals and database sources are to be included where:

- Open access full text e.g. Cochrane, PLOS Medicine;
- Full text via NHS ATHENS authentication (national content only) e.g. Lancet;
- Freely available abstract.

NB: The Medicines Awareness Service should link to full text where freely available. For gated full text please link to abstract. Highlighting an abstract of a paper is sufficient to raise awareness and allows the user to request or pursue further information/ access if required.

NB: News agencies, for example Reuters Health, may highlight key primary research content.

No journal is excluded. Journals included on the source list and checked daily (see Appendix A) have been identified by UKMI as the key journals featuring key medicine-related studies, including the Big 5 – the Lancet, the Journal of the American Medical Association, the British Medical Journal, Annals of Internal Medicines and the New England Journal of Medicine.

Content from other journals identified via press agencies comes under 3.3.7 Media and commentaries definition.

3.3.6.POLICY

UK government health policy with a direct relevance to medicines and prescribing.
For example, policy frameworks and consultation on legislation changes relevant to medicines from the Department of Health and the NHS England.

3.3.7.MEDIA AND COMMENTARIES

Media: Press releases and media news stories relevant to health care provision in the NHS, i.e. addressing a disease or condition or describe a situation that may affect clinical staff or senior managers.

To also include promotion of updated NICE guidance and quality standards linking to the update / change page e.g. http://www.nice.org.uk/guidance/qs10/chapter/Update-information.

Commentaries: Editorial, review and comment articles from journals. Media and commentaries content is to be included to cover one of the following purposes:

- Health news stories in the popular media to allow clinical staff to anticipate patient queries and misconceptions and identify the evidence-based responses e.g. BBC Health News, Behind the Headlines from NHS Choices
- Organisational draft publications and consultations, news feeds and press releases to stay abreast of new or pending developments and publications. For example, developments in the NHS, the pharmaceutical industry, and elsewhere may affect NHS professionals without producing, or before they produce more formal documents; NICE Appraisal Consultation Documents
- Topical news stories and press releases from key organisational websites raise awareness of issues that may have an early impact on their work. These include:

- ‘Latest News’ sections from key NHS, government and pharmacy sites e.g. National Audit Commission, Care Quality Commission, Health Protection Agency;
- Organisational commentary on previously published / bibliographic evidence e.g. the British Medical Association; Department of Health statements on pharmacy, medicines, prescribing and major NHS issues.
- New trials, licence indications and product launches in the UK and significant EU marketing authorisation from manufacturers press releases, Medicines and Healthcare products Regulatory Agency and European Medicines Agency.

- News agencies, for example BBC Health News and Reuters Health, are to be reviewed daily for key research and trials highlighted by national newspapers including those where the abstract or full text isn’t available.
  NB: Where possible the record needs to link to original source; news agency can be included under ‘related URL’ field if appropriate.
- Editorials, selected (non-systematic) reviews and guidelines which help contextualise new trials, new license indications, product launches or medicine-related developments in the treatment of particular diseases.

NB: Media and commentaries content will only be available via the NICE Evidence Search for three months from publication.

3.3.8.OTHER EVIDENCE

The above sections represent the main areas of content to be highlighted. However, it is recognised that there may be occasions when other evidence based current awareness content are considered to be important and of relevance to the medicines and prescribing communities.

These may relate to, for example, high quality QIPP examples, patient decision aids, newly published care pathways or learning materials that may from time to time be considered to be of significant interest to highlight in the daily service.

These include:

- Care pathways
- Drug horizon scanning
- Drug regulatory and marketing
- Evidence-based management reports
- Patient decision aids
- Other economic evaluations
- Drug/Medicines management
- Audit report
- Effective practice examples
- Implementation support tools
- Learning materials

- Quality measures
- Patient information
- Population intelligence
- Population needs assessment

4. Exclusion criteria

Criteria for the exclusion of content in the medicines awareness service:

- Sources and content that require membership or subscriptions outside NHS ATHENS authentication (excluding open access abstract sources or research stories included under Media and Commentaries).
- Content that relates exclusively to surgery, social care or dentistry (without a large medicines and prescribing component) and tropical medicine content unless it has a significant impact on UK public health.
- Non-UK healthcare-based studies, especially economic analyses where UK practice is very different so that data are unlikely to be applicable or comparable.
- Animal, in-vitro or early phase studies unless they have been the focus of significant media attention.
- International sources on uncommon conditions.
- News items specific to clinical practice in other countries.
- Information provided in a language other than English.
- News of prizes, scholarships, book launches and (outside of the Department of Health) appointments are excluded.
- Calls for volunteers or study participants.
- Events.
- Content identified as part of the NICE Medicines Management specialist collection that falls outside of the above inclusion criteria.

5. Prioritisation criteria for the Medicines Awareness Weekly

In addition to the daily awareness service, users have the choice of a more compact weekly awareness service, content for which is identified by a NICE MPP pharmacist editor from the previous week's Medicines Awareness Daily.

UKMI is responsible for ranking each Medicines Awareness Daily record 1 to 3 (see section 2.2.2). On a weekly basis, MPP pharmacist editors work on a rota to review the recommended content and select prioritised records from the daily service for inclusion in the Medicines Awareness Weekly. The aim is to select the most important and useful records from the above information categories, while keeping the content to a manageable amount for subscribers. Not all records from the daily service can be included in the weekly service; content is restricted to approximately 30 records.

The fundamental criterion to support the prioritisation of content for the weekly service can be described as the 'Common Sense Test' which asks the question: 'Is it important for a healthcare professional whose practice involves medicines to be made aware of this piece of information as part of their general current awareness?'.

The following record types are to be included in the Medicines Awareness Weekly:

- Safety information, for example Drug Safety Updates, drug withdrawals or licence changes relating to safety.
- NICE products (final versions) which relate to medicines and prescribing practice.
- Medicines information / advice e.g. changes to practice, with high relevance to practice or very commonly prescribed drugs

In addition, other records will be selected for the Medicines Awareness Weekly; these include

- Significant policy changes and developments, for example QOF changes
- Important records relating to medicines, prescribing and evidence-based practice, for example major pieces of research that require, or have the potential to require, changes in practice; issues relating to clarity or availability of research information; review articles relating to matters such as shared decision-making; launches of new medicines
- Information that is relevant to substantial media interest/awareness, for example, key Behind the Headlines articles.

The following record types are to be excluded from the Medicines Awareness Service:

- Draft guidance
- Information on new drugs not currently available for use in practice e.g. from MHRA, EMA.

5.1. Medicines Evidence Commentaries

Medicines Evidence Commentaries, a weekly publication from MPP providing information on new evidence on medicines currently in use for NHS commissioners, prescribers and prescribing managers is included in the Medicines Awareness Weekly.

6. Governance

Strategic input into the content strategy, including agreement of the inclusion, exclusion and prioritisation criteria and promotional and marketing activities sits with the Evidence Information Services team. Additional input into the strategy and supporting processes can also come from UKMI and MPP.

The source list in Appendix A and the website guidance notes in the Standard Operating Procedures will be maintained with up-to-date information when necessary e.g. removal of archived organisations or update of instructions on how to find information on the website.

New organisations, whose information products fit the criteria and merit inclusion in the awareness service, and excluded sources will be reviewed by the Evidence Information Services team and agreed with UKMI.

7. Syndication

Content identified via the Medicines Awareness Service will be made available via the NICE syndication service.

Syndication allows third party organisations in the public and private sector apply and be issued with a licence to take content from NICE and NICE Evidence and embed this content within their own online systems and services within the UK.

In terms of Evidence Search, NICE proposes to syndicate the Evidence Search index to third parties so that a user on a third party site is able to search and find this content and see it in exactly the same way as if they were searching NICE Evidence Search itself. This will expand the dissemination of the Evidence Search index, including Medicines Current Awareness content, as widely as possible.

Appendix A - Source list

List of sources (organisation websites) to be checked on a daily basis

Source	Information types
All Wales Medicines Strategy Group	Guidance and Advice; Policy
Annals of Internal Medicine	Primary Research
Arthritis & Rheumatism	Primary Research
Audit Commission	Media and Commentaries
BBC Health News	Primary Research, Media and Commentaries
BioSpace	Primary Research, Media and Commentaries
British Journal of Psychiatry	Primary Research
British Medical Journal	Primary Research
British National Formulary	Guidance and Advice
Canadian Agency for Drugs and Technologies in Health	Systematic Reviews
Care Quality Commission	Media and Commentaries
Central Alerting System	Safety Alerts; Media and Commentaries
Circulation	Primary Research
Department of Health	Policy
Diabetes Care	Primary Research
Drug and Therapeutics Bulletin	Evidence Summaries
e-Health insider	Media and Commentaries
European Heart Journal	Primary Research
European Medicines Agency	Safety Alerts; Media and Commentaries
electronic Medicines Compendium	Guidance and Advice
General Pharmaceutical Council	Media and Commentaries
Health and Social Care Information Centre	Media and Commentaries
Heart	Primary Research
JAMA Internal Medicine	Primary Research
JAMA Neurology	Primary Research
JAMA Psychiatry	Primary Research
Journal of the American Medical Association	Primary Research
Journal of Clinical Oncology	Primary Research
Kantar Media Intelligence Health News	Primary Research, Media and Commentaries
The King's Fund	Media and Commentaries
Lancet	Primary Research
Lancet Diabetes & Endocrinology	Primary Research
Lancet Infectious Disease	Primary Research
Lancet Neurology	Primary Research
Lancet Oncology	Primary Research
Lancet Psychiatry	Primary Research
Lancet Respiratory Medicine	Primary Research
Medicines and Healthcare products Regulatory Agency	Safety Alerts; Media and Commentaries
Midlands Therapeutics Review & Advisory Committee	Evidence Summaries

Source	Information types
MIMS	Media and Commentaries
Monitor	Media and Commentaries
National Audit Office	Media and Commentaries
National Institute for Health and Care Excellence	Guidance and Advice; Evidence Summaries; Media and Commentaries
National Institute for Health Research	Evidence Summaries
National Pharmacy Association	Media and Commentaries
NetDoctor	Media and Commentaries
New England Journal of Medicine	Primary Research
NHS Choices	Media and Commentaries
NHS Confederation	Media and Commentaries
NHS England	Policy
NHS Networks	Media and Commentaries
NIHR Health Technology Assessment Programme	Systematic Reviews
Pharmaceutical Services Negotiating Committee	Media and Commentaries
Pharmaceutical Journal	Guidance and Advice
PharmaTimes	Media and Commentaries
Primary Care Commissioning	Policy
Public Health England	Policy
Royal Pharmaceutical Society	Media and Commentaries
Scottish Intercollegiate Guidelines Network	Guidance and Advice
Scottish Medicines Consortium	Guidance and Advice
Thorax	Primary Research
UKMI – regional centres	Evidence Summaries
US Food and Drug Administration	Safety Alerts; Media and Commentaries

Appendix B – Information type definitions

1. GUIDANCE AND ADVICE

Type	Description	Example
Guidance	Newly published or updated systematically developed statements to guide decisions about appropriate health and social care to improve individual and population health and wellbeing.	National and accredited guidance producers. Scottish Intercollegiate Guidelines Network guidelines; NICE guidance; Royal College guidance
Drug best practice guidance	Other newly published or updated guidance and recommendations to support the optimal use of medicines.	NICE - Technology Appraisals; All Wales Medicines Strategy Group – Appraisal recommendations; Scottish Medicines Consortium – Advice
Commissioning guides	Commissioning resources to inform local NHS planning and decision-making	NICE guides for commissioners
Drug prescribing	Technical information to support the safe prescribing of medicines.	Significant product licence changes or significant changes to drug monographs. British National Formulary and British National Formulary for Children – prescribing information; electronic Medicines Compendium – Summary of Product Characteristics and Patient Information Leaflets

2. SAFETY ALERTS

Type	Description	Example
Safety alerts	Safety, alerts and recalls content covering patient safety, medical device alerts, drug alerts and drug withdrawals	Medicines and Healthcare products Regulatory Agency; European Medicines Agency; US Food and Drug Administration

3. SYSTEMATIC REVIEWS

Type	Description	Example
Systematic reviews	Selected systematic reviews/ meta-analysis of medicines or lifestyle interventions.	Cochrane Database of Systematic Reviews
Health technology assessments	Assessments determining the clinical and cost effectiveness of a health technology.	National Institute for Health Research Health Technology Assessment

4. EVIDENCE SUMMARIES

Type	Description	Example
Evidence summaries	Summaries of the best available evidence to inform local NHS planning and decision-making.	NICE Medicines and Prescribing Programme Evidence Summaries; Clinical Knowledge Summaries; NIHR Dissemination Centre Signals; UKMI regional evidence summaries e.g. Regional Drug and Therapeutics Centre
Evidence updates	Summaries of newly published selected evidence in relation to accredited guidance. Produced by NICE they highlight where new evidence has been published that might generate a future change in practice.	Evidence Updates from NICE Evidence Resources
Medicines evidence commentaries	A weekly publication from NICE Medicines and Prescribing Centre, providing information on new evidence on medicines currently in use for NHS commissioners, prescribers and prescribing managers.	
Medicines Q&A	UKMI produced evidence-based, quality assured answers to common or unusual medicines related enquires made to local medicines information services.	

5. PRIMARY RESEARCH

Type	Description	Example
Randomised controlled trials	The results of selected Phase 3 and 2 randomised controlled trials into medicines (or lifestyle interventions involving medicines or pharmacy) pertaining to conditions and diseases relevant to UK clinical practice.	Open access to full text or abstract, either in the public domain or via NHS ATHENS authentication.
Other primary research	Articles and reports of newly published or updated primary research which is not a RCT or ongoing or unpublished research.	As above
Ongoing or unpublished research	Ongoing or unpublished research including recruiting trials	As above

6. POLICY

Type	Description	Example
Policy	UK government health policy with a direct relevance to medicines and prescribing.	Department of Health, NHS Primary Care Commissioning, Welsh Assembly Government

7. MEDIA AND COMMENTARIES

Type	Description	Example
Media and commentaries	Press releases and news stories relevant to health care provision in the NHS; organisational draft publications, consultations and commentary; Editorials, selected (non-systematic) reviews	Journal commentaries, NHS Choices Behind the Headlines; National Audit Commission; Care Quality Commission; Health Protection Agency; MIMS; BBC Health News; Reuters Health

8. OTHER EVIDENCE

Type	Description	Example
Care pathways	Care pathways both describe an ideal model of care for a given condition and provide a way of recording relevant details of what actually happened during the care of a specific individual.	NICE pathways; Department of Health
Drug horizon scanning	Information to support the managed entry of new medicines to the NHS	National Horizon Scanning Centre – New and emerging Technology briefings; Medicines and Prescribing Centre – New Medicines publications; New Drugs Online – monographs on drugs in clinical development
Drug regulatory and marketing	Information on changes to market authorisations and licensed uses of medicines	Medicines and Healthcare products Regulatory Agency – Regulatory Guidance
Evidence-based management reports	Evidence-based reports or briefings which address key issues in the management of healthcare, public health or social care.	The King's Fund, NHS Improvement
Patient decision aids	Products designed to aid communication and decision making between patients and other service users, and health and social care professionals.	Medicines and Prescribing Centre patient decision aids; NHS Direct patient decision aids,

Type	Description	Example
Other economic evaluations	Comparative analysis of alternative courses of action in terms of both their costs and their benefits.	NHS Economic Evaluation Database
Drug/medicines management	Systems and processes to support best practice in the use of medicines.	Department of Health – Medicines and Pharmacy content; NICE Medicines Management collection
Audit reports	The outcomes of national audits and equivalent initiatives.	National audits reported by the Information Centre of the Royal Colleges
Effective practice examples	Local, regional or national examples of practice that have been quality assured and found to be effective to deliver evidence-based health or social care or in implementing health and social care policy.	
Implementation support tools	Materials developed specifically to support the uptake and use of evidence in health and social care.	NICE implementation support tools
Learning materials	Selected evidence-based, high quality learning materials.	NICE British Medical Journal learning modules; Medicines and Prescribing Centre learning materials
Quality measures	A measurable element of performance which address process and/or outcomes of health and social care.	NICE quality standards and Quality and Outcomes Framework menu items
Patient information	Publications, aimed at a lay audience.	Patient UK, Medicines for Children, Patient Information Leaflets
Population intelligence	To be applied to statistics, numerical information and data presented in ways to support population health. This type covers both tools and reports. It is suggested that this type may need to be excluded once Public Health England is in place as population intelligence should fall within its remit. No new sources/records should be added with this type.	
Population needs assessments	To be applied to publications which aim to measure the extent and nature of the need of a particular target population in order to make a response to that need.	

Appendix C – Information type mapping to NICE Evidence Search

All the content identified for the Medicines Awareness Service can be found on the NICE Evidence Search via the 'Medicines Current Awareness' Evidence Type filter (Media and Commentaries content limited to last 3 months).

In addition the table below lists the mapping of the information types to the other NICE Evidence Search Evidence Types.

New UKMI Information Types	NICE Evidence Search Evidence Types mapping
Guidance	Guidance
Drug best practice guidance	Prescribing and Technical Information
Commissioning guides	Implementation support
Drug prescribing	Prescribing and Technical Information
Systematic reviews	Systematic Reviews
Health technology assessments	Health Technology Assessments
Evidence summaries	Evidence Summaries
Medicines Evidence Commentaries	Evidence Summaries
Evidence Updates	Evidence Summaries
Eyes on Evidence commentaries	Evidence Summaries
Medicines Q & A	Evidence Summaries
Safety alerts	Safety Alerts
Policy	Policy and Stratgey
Media and Commentaries	No mapping
Randomised controlled trials	Primary Research
Other primary research	Primary Research
Ongoing or unpublished research	Ongoing Trials
Care pathways	Guidance
Drug horizon scanning	Horizon Scanning
Drug regulatory and marketing	Prescribing and Technical Information
Evidence-based management reports	Evidence Summaries
Patient decision aids	Information for the Public
Other economic evaluations	Economic Evaluations
Drug/medicines management	No mapping
Audit reports	Audit and Inspection Reports
Effective practice examples	Case studies
Implementation support tools	Implementation support
Learning materials	Implementation support
Quality measures	Quality Indicators
Patient information	Information for the Public
Population intelligence	No mapping
Population needs assessments	No mapping

Appendix D – Supplementary guidance notes for including NICE content in the Medicines Awareness Daily (Feb 2015)

Linking to NICE documents

Document hyperlinks should be to the NICE website landing page, not to copies or subsections of the product.

Summary field

The short summary is to use the summary given on the NICE website, avoiding any change in wording and including details of superseded guidance where these are made explicit on the NICE website.

Title, format and URL

In order for NICE records included in the MAD to merge with NICE records in the Evidence Search, please use the following rules for title, format and URL. This avoids duplication of results in the Evidence search.

For new NICE products, please find the relevant Evidence Search entry to check the title, format and URL.

NICE Guidance (all types) and advice

Format and URL

Use the URL to the main landing page of published guidance. For example, for NG1 Gastro-oesophageal reflux disease: recognition, diagnosis and management in children and young people the URL is:

http://www.nice.org.uk/guidance/ng1

This URL structure is consistent for all types of guidance, such as HSTs and advice such as KTTs.

Title

Use the title displayed on the landing page and add a suffix of " – guidance" combined with the guidance ID in brackets. For example, the title for NG1 would be:

Gastro-oesophageal reflux disease: recognition, diagnosis and management in children and young people - guidance (NG1)

NICE Quality Standards

Format and URL

Use the URL to the main landing page of published quality standards. For example, QS57 on neonatal jaundice the URL is:

http://www.nice.org.uk/guidance/QS57

This URL structure is consistent for all quality standards.

Title

Use the title displayed on the landing page and add a suffix of " – quality standard " combined with the standard ID in brackets. For example, the title, with the suffix for QS57 would be:

Neonatal jaundice - quality standard (QS57)

Commissioning guides

Format and URL

Commissioning guides, identified by CMG id, are being replaced by support for commissioning published alongside quality standards.

For the new commissioning guides, go to the resources section of the quality standard and use the PDF download URL. For example, the resource section for the QS51 on autism can be found at https://www.nice.org.uk/guidance/qs51/resources.

The PDF download URL for the commissioning guide for QS51 is:

https://www.nice.org.uk/guidance/qs51/resources/qs51-autism-support-for-commissioning2

NB: For old style commissioning guides that have a CMG id, use the URL to the main landing page of the guides. For example, CMG47 on Diagnosis and management of the epilepsies in adults, children and young people the URL is:

http://www.nice.org.uk/guidance/CMG47

Title

For both types of commissioning guide, use the title displayed on the landing page and add a suffix of " – support for commissioning " combined with the standard ID in brackets. For example, the title for CMG47 and QS51 would be:

Diagnosis and management of the epilepsies in adults, children and young people - support for commissioning (CMG47)

Autism - support for commissioning (QS51)

Evidence summaries - unlicensed/off-label medicines

Format and URL

Use the URL to the main landing page of published ESUOMs. For example, for ESUOM30 Pouchitis: rifaximin the URL is:

http://www.nice.org.uk/advice/ESUOM30

This URL structure is consistent for all ESUOMs.

Title

Use the title displayed on the landing page and add a suffix of " – evidence summary unlicensed/off label medicine " combined with the standard ID in brackets. For example, the title for ESUOMN30 would be as follows:

Pouchitis: rifaximin - evidence summary unlicensed/off label medicine (ESUOM30)

Evidence summaries – new medicines

Format and URL

Use the URL to the main landing page of published ESNMs. For example, for ESNM42 Psoriatic arthritis in adults: certolizumab pegol the URL is:

http://www.nice.org.uk/advice/ESNM42

This URL structure is consistent for all ESNMs.

Title

Use the title displayed on the landing page and add a suffix of " – evidence summary new medicines " combined with the standard ID in brackets. For example, the title for ESUOMN30 would be as follows:

Psoriatic arthritis in adults: certolizumab pegol - evidence summary new medicines (ESNM42)

MPC Medicine practice guidelines

Format and URL

Use the URL to the main landing page of published MPG guidance. For example, for MPG1 developing and updating local formularies the URL is:

http://www.nice.org.uk/guidance/MPG1

This URL structure is consistent for all MPG documents.

Title

Use the title displayed on the landing page and add a suffix of " – guidance " combined with the guidance ID in brackets. For example, the title for MPG1 would be as follows:

Developing and updating local formularies - guidance (MPG1)

Eyes on Evidence Commentaries

Format and URL

Use the URL to the ARMS version of each individual Eyes on Evidence Commentaries.
These are provided by email from Carrie Thomson prior to the Eyes On Evidence monthly bulletin, or can be found by running a search on NICE Evidence and right clicking 'Copy shortcut' on the search result. For example, for the June 2014 Eyes on Evidence commentary on Prescriptions for anxiolytics and hypnotics and risk of death, the URL is:

http://arms.evidence.nhs.uk/resources/hub/1035846/attachment

Title

Use the title displayed in NICE Evidence, using the prefix “Eyes on Evidence : ” and the commentary title. For example,

Eyes on Evidence : prescriptions for anxiolytics and hypnotics and risk of death

Source

National Institute of Health and Care Excellence

QIPP examples

Format and URL

Use the URL to the ARMS version. These can be found by running a search on NICE Evidence and right clicking ‘Copy shortcut’ on the search result.

For example, for the June 2014 QIPP example on Wireless working in hospitals: Improving efficiency and safety of out-of hours, the URL is:

http://arms.evidence.nhs.uk/resources/qipp/978946/attachment

Title

Use the title displayed in NICE Evidence. For this example, the title would be:

Wireless working in hospitals: Improving efficiency and safety of out-of hours

Source

To use the organisation name displayed in NICE Evidence. For this example, the Source would be:

Nottingham University Hospitals NHS Trust

Appendix D

Medicines Awareness Service: Content identification, record creation and publication of the Medicines Awareness Daily

Standard Operating Procedure

Document History

Version no.	Date	Name	Summary of changes
0.1	25.01.2013	[redacted]	First draft (no appendices)
0.2	06.02.2013	[redacted]	Appendix 3 and 4 drafted
0.3	12.02.2013	[redacted]	Comments from [redacted]
0.4	26.02.2013	[redacted]	Comments and clarifications from t/c with UKMI
0.5	01.03.2013	[redacted]	Amended to reflect new EpiServer template; addition of content inclusion guidance appendices.
0.6	15.03.2013	[redacted]	Incorporation of comments from [redacted], [redacted], [redacted] and UKMI from training sessions.
1.0	02.04.2013	[redacted]	Correction of login URL.
1.2	03.07.2013	[redacted]	Document review. Editorial changes; changes to reflect EpiServer technology change requests e.g. limit short summary to 280 characters; inclusion of review as an information type.
1.3	18.11.2013	[redacted]	Feedback from V1.2 from UKMI
1.4	11.02.2015	[redacted]	Document review and update; update to UKMI Comment sections to reflect use for related links and MHRA statement; updated Appendix B guidance notes for content inclusion by source
1.5	03.02.2016	[redacted]	Added content section and updated source list
1.6	17.08.2016	[redacted]	Added MIMS as a new media and commentaries resource following confirmation from [redacted] it was to be included. Removed references to Eyes on Evidence.

Author	[redacted]
Audience	UK Medicines Information (UKMI) Information Specialists

Purpose

The purpose of this SOP is to assist the UKMI Medicines Information Specialist in the creation and delivery of the NICE Medicines Awareness Daily. This includes the

steps to identify content and create, quality assure and publish records to support the delivery of a high quality NICE Medicines Awareness Service.

Who's who

Role title	Responsibility
MIS	Medicines Information Specialists responsible for creating content
SE	Senior Editor (Medicines Information Specialist) responsible for quality assuring content prior to publication.

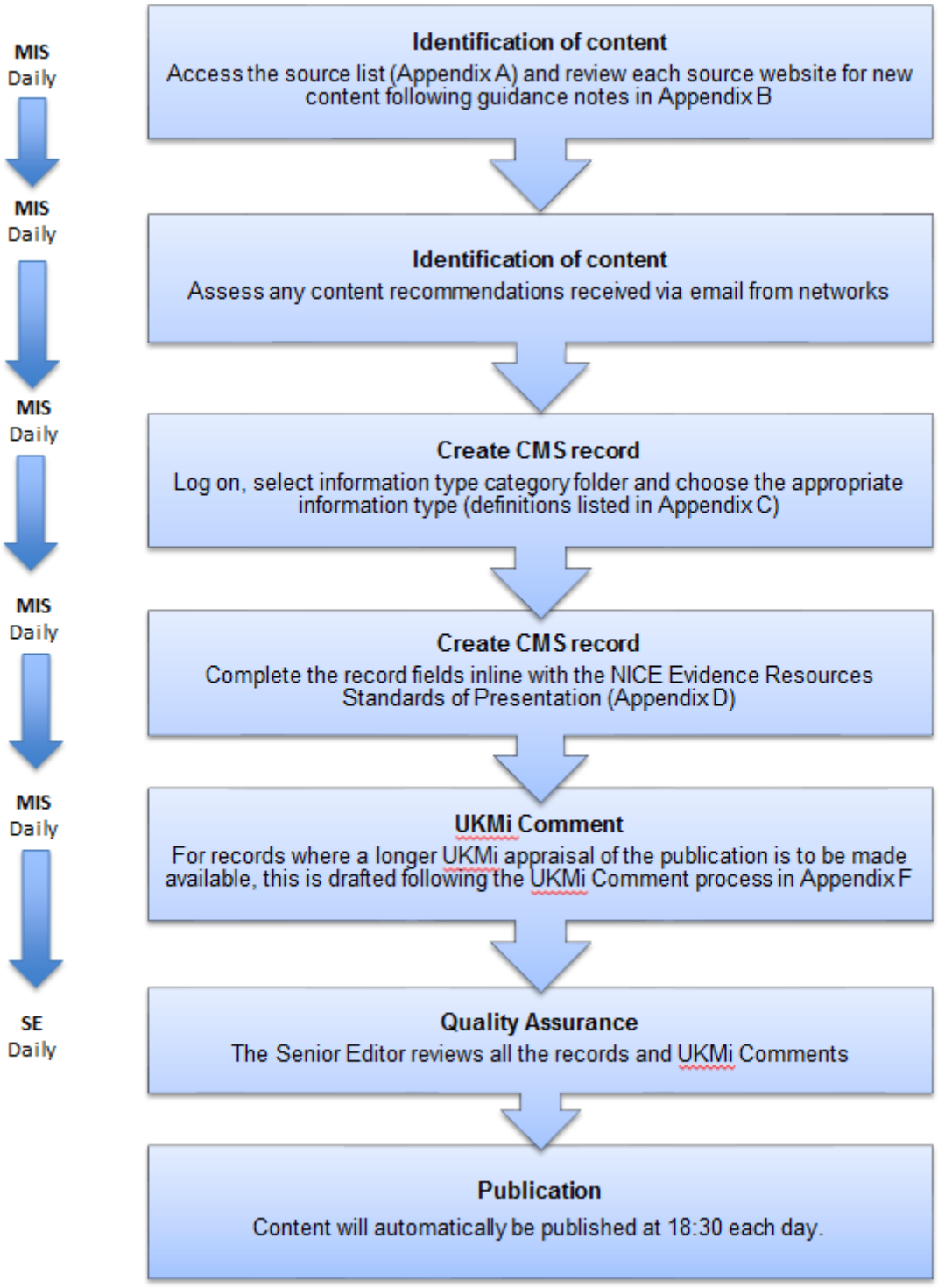
Acronyms

MAD	Medicines Awareness Daily
MAW	Medicines Awareness Weekly

Resources

- NICE Medicines Awareness Content Strategy

Flowchart


MIS
Daily
Identification of content
Access the source list (Appendix A) and review each source website for new content following guidance notes in Appendix B
MIS
Daily
Identification of content
Assess any content recommendations received via email from networks
MIS
Daily
Create CMS record
Log on, select information type category folder and choose the appropriate information type (definitions listed in Appendix C)
MIS
Daily
Create CMS record
Complete the record fields inline with the NICE Evidence Resources Standards of Presentation (Appendix D)
MIS
Daily
UKMi Comment
For records where a longer UKMi appraisal of the publication is to be made available, this is drafted following the UKMi Comment process in Appendix F
SE
Daily
Quality Assurance
The Senior Editor reviews all the records and UKMi Comments
Publication
Content will automatically be published at 18:30 each day.

Process table

	Action	Responsibility
A	**Identification of content for the NICE Medicines Awareness Service**	
1.	On a daily (Mon-Friday) basis, MIS accesses the source list and reviews each source website for new content following the guidance notes for relevant content. (See **Appendix A** for source list and **Appendix B** for guidance notes for each source website)	MIS
2.	New content can be identified by checking the publication date. If the item is not dated the MIS can run a search on NICE Evidence Search filtered by Type of Information: Medicines Awareness to see if it has already been included.	MIS
3.	Access any content received from external contacts via email.	MIS
B	**Create CMS record**	
4.	Go to www.medicinesresources.nhs.uk/edit and login using your username and password.	MIS
5.	In the left hand navigator panel click on the '**Medicines Awareness** Service' folder to expand. NB: Folders are expanded by clicking on the + sign next to the name. Select the relevant information type category folder, expand, choose the granular information type. (See **Appendix C** for Information Type definitions) Right click on the information type folder name and select 'Create New'.	MIS
6.	In the right hand navigator panel the '**Create new page**' template has opened. Click 'Create' next to **UKMI Medicines Awareness**.	MIS
	Complete the following record fields in line with the NICE Evidence Resources Standards of Presentation. (See **Appendix D** for Standards of Presentation)	
7.	In the 'Information' tab, in the Name field add • **Title** – free text Mandatory Field This is the title which appears in the Medicines Awareness Service email and in the NHS Evidence search result, limited to 255 characters. This is to be the title of the document or article and	MIS

	should NOT be edited or prefixed to include, for example, the source name. The only exceptions are: • Truncation of titles which exceed 255 characters (field limit) e.g. primary research titles. Truncate to beginning section of title where possible/comprehensible • SPC's are preceded by Revised/New Product • Rewrite sensationalist media headlines to factual description.	
8.	In the Start publish field add • **Publication date** - calendar Mandatory Field This is the date the document or article was published. This should be the ePublication date for online content. Complete the Stop Publish field for Medicines Q&As only.	MIS
9.	• **Source** – drop down list Mandatory Field Type ahead functionality	MIS
10.	• **Speciality** – checkboxes More than one tag can be applied to a record but only to be used where necessary. This tagging informs the content that appears in the MAW where the subscriber has personalised their content using these categories. (See **Appendix E** for full list of Speciality categories)	MIS
11.	• **UKMI Medicines Awareness Weekly relevancy score** Mandatory Field 1 – 3 relevancy rating for potential inclusion in the Medicines Awareness Weekly email: 1 - important items which are recommended for inclusion 2 - items of borderline significance 3 - items not recommended for inclusion	MIS
12.	• **Eyes on Evidence** Function no longer used.	MIS
13.	• **Geographical coverage** – drop down list Default set to blank. Use UK/International values for guidance records.	MIS

14.	In the 'Article Summary' tab • **Short summary** – free text Factual description of publication/article is limited to 280 characters. This is approximately 3.5 lines in the Short Summary field and should be written in line, i.e. with no new lines or bullet points. This is used as the teaser text in the Medicines Awareness Service and is not meant to be an appraisal of the publication/article. The short summary is to be used to clearly attribute comments/recommendations/opinions to the author. Any copied content is to be pasted using 'Paste unformatted' to ensure the teaser text style remains consistent.	MIS
15.	• **UKMI Comment** – free text For publications/articles where a longer UKMI Comment is to be made available, this is drafted following the agreed UKMI Comment Process. Any copied content is to be pasted using 'Paste unformatted'. Related links are to be added to the UKMI Comment using the standard text: "UKMI have identified the following resources which may also be of interest: • xxx" NB: For inclusion of EMA PRAC reports where no MHRA guidance has been published, the UKMI Comment function should include the following statement: "This recommendation has been published by EMA and there is currently no related MHRA guidance available to assess implications for practice in the UK". (See **Appendix F** for the UKMI Comment process)	MIS
16.	In the 'Article Content' tab enter the document/article resource link(s). In the field **Resource Links** click the browse button […]. This opens the 'Multi Link Selection' dialog box. Click the browse button […], this opens the 'Link Properties' dialog box with tab options Webpage, Document or Email. **Webpage**	MIS

	'Page on another Web site' is pre-selected. Enter the web address in the address box ensuring it is pre-fixed with http://. Click Ok. In the 'Multi Link Selection' dialog box click '**Add**'. The link should now display in the Link table. **Document on another website** Select 'Document on another Web site' and enter the web address in the address box ensuring it is pre-fixed with http://. Click Ok. In the 'Multi Link Selection' dialog box click '**Add**'. The link should now display in the Link table. **Document on this website** To be used to upload documents not available on a website, for example, UKMI authored documents; h/c professional communications. Select 'Document on this Web site' and click the browse button […]. This opens a new dialog box. Select Create folder or Add new file. In the 'Multi Link Selection' dialog box click '**Add**'. The link should now display in the Link table. In line with the content strategy, the Medicines Awareness Service should link to open access content (abstract or full text) rather than pages which require log-ins.	
17.	The primary resource should use the webpage/site address as the clickable text. The clickable text for any additional resource links can either be the web address or have text added using the 'Clickable text' box.	MIS
18.	Manage the resource links using the Move Up / Move Down arrows.	MIS
19.	In the Link table, use the 'Move down/Move up/delete' buttons as needed. NB: Ensure the top link is the primary URL which links to the original publication/article. Related links can be included below. Click '**Update**'. The Resource Links box should now reflect the number of resources being linked to.	MIS
20.	In the 'Advanced Information' tab set the	MIS

	• **Created** – calendar Default to today's date. NB: Ignore all other fields in this tab.	
21.	Save the record by using one of the options: **Save and View** – this displays a preview of the webpage, useful for rendering of UKMI Comment **Save and publish** – to include the record in the Medicines Awareness Daily NB: **Cancel** – Permanently deletes the record.	MIS
22.	Make a final check that the record is in the correct Information Type folder. To move a record click on the record name in the left hand navigation panel and drag and drop to the new information type folder.	MIS
	NB: The order in which the content is listed in the email is automatically generated. Records do not need to be ordered by the MIS.	
C	**Quality Assurance**	
23.	All records are to be reviewed daily (Mon- Friday) before content is published in line with **Appendix D** – NICE Evidence Resources Standards of Presentation.	
24.	In the left hand navigator panel click on the 'Medicines Awareness Administration' folder to expand. Expand folder 'Medicines Awareness Emails' and click on **'Medicines Awareness Daily_template'.**	SE
25.	Click the edit tab. In Information tab set 'Preview date' to today's date to preview the content for the last 24 hours. Complete the 'To email' field with an email address which is both subscribed to the service and has ALL subscription options selected. Click 'Save and View' to see a preview of the content for that day's Medicines Awareness Service. Any changes can be made by following the steps in section E.	SE
26.	Confirm by email to MIS that QA has been completed.	SE
D	**Publication**	
27.	The content will automatically publish at 20:00 each day (BST).	MIS

	Any record which has not been saved using the 'Save and Publish' function before the Medicines Awareness Daily email is sent will automatically be included in the next day edition. For days where there is no content or records the Medicines Awareness Daily email will not be sent e.g. Bank Holidays.	
E	**Edit / Delete records**	
28.	To edit or delete a record, find it in the left hand navigation panel under the 'Medicines Awareness Service folder. Expand the folders until you can see the record titles listed under each Information Type, and then right click on the record. This gives you the option to edit or delete the record. Alternatively you can use the search box at the bottom of the left hand navigation panel. Make the changes and click 'Save and publish'.	MIS, SE
29.	To re-publish the record in the Medicines Awareness Daily the 'Created date' needs to be updated to today's date following step 20. NB: Records are only to be re-published where there is a significant change in detail. Small amendments will be picked up in the feed to NICE Evidence search on a daily basis and do NOT need to be re-published in the Medicines Awareness Daily.	MIS, SE
F	**Issue Reporting**	
30.	Any technical issues experienced whilst following this SOP are to be reported by contacting the NICE Enquiries (helpdesk): via email: [redacted] via telephone: [redacted] The helpdesk is available (office hours) 9-5pm Mon-Fri excluding public holidays. Please ensure that any queries are marked **UKMI Editor - Medicines Awareness Service** in the subject field to ensure that your report is immediately escalated to the correct technical team. Please include as much detail of the issue, the user journey leading to the issue and screen shots where possible to assist with the rapid diagnosis of the issue.	MIS, SE
G	**Log Out**	
31.	To log out, click the logout icon at the top of the left hand navigation panel, second row, 5th icon showing a green arrow and open door.	MIS, SE

APPENDIX A – Source list

List of sources (organisation websites) to be checked on a daily basis

Source	Information types
All Wales Medicines Strategy Group	Guidance and Advice; Policy
Annals of Internal Medicine	Primary Research
Arthritis & Rheumatism	Primary Research
Audit Commission	Media and Commentaries
BBC Health News	Primary Research, Media and Commentaries
BioSpace	Primary Research, Media and Commentaries
British Journal of Psychiatry	Primary Research
British Medical Journal	Primary Research
British National Formulary	Guidance and Advice
Canadian Agency for Drugs and Technologies in Health	Systematic Reviews
Care Quality Commission	Media and Commentaries
Central Alerting System	Safety Alerts; Media and Commentaries
Circulation	Primary Research
Department of Health	Policy
Diabetes Care	Primary Research
Drug and Therapeutics Bulletin	Evidence Summaries
e-Health insider	Media and Commentaries
European Heart Journal	Primary Research
European Medicines Agency	Safety Alerts; Media and Commentaries
electronic Medicines Compendium	Guidance and Advice
General Pharmaceutical Council	Media and Commentaries
Health and Social Care Information Centre	Media and Commentaries
Heart	Primary Research
JAMA Internal Medicine	Primary Research
JAMA Neurology	Primary Research
JAMA Psychiatry	Primary Research
Journal of the American Medical Association	Primary Research
Journal of Clinical Oncology	Primary Research
Kantar Media Intelligence Health News	Primary Research, Media and Commentaries

Source	Information types
The King's Fund	Media and Commentaries
Lancet	Primary Research
Lancet Diabetes & Endocrinology	Primary Research
Lancet Infectious Disease	Primary Research
Lancet Neurology	Primary Research
Lancet Oncology	Primary Research
Lancet Psychiatry	Primary Research
Lancet Respiratory Medicine	Primary Research
Medicines and Healthcare products Regulatory Agency	Safety Alerts; Media and Commentaries
Midlands Therapeutics Review & Advisory Committee	Evidence Summaries
MIMS	Media and Commentaries
Monitor	Media and Commentaries
National Audit Office	Media and Commentaries
National Institute for Health and Care Excellence	Guidance and Advice; Evidence Summaries; Media and Commentaries
National Institute for Health Research	Evidence Summaries
National Pharmacy Association	Media and Commentaries
NetDoctor	Media and Commentaries
New England Journal of Medicine	Primary Research
NHS Choices	Media and Commentaries
NHS Confederation	Media and Commentaries
NHS England	Policy
NHS Networks	Media and Commentaries
NIHR Health Technology Assessment Programme	Systematic Reviews
Pharmaceutical Services Negotiating Committee	Media and Commentaries
Pharmaceutical Journal	Guidance and Advice
PharmaTimes	Media and Commentaries
Primary Care Commissioning	Policy
Public Health England	Policy
Royal Pharmaceutical Society	Media and Commentaries
Scottish Intercollegiate Guidelines Network	Guidance and Advice

Source	Information types
Scottish Medicines Consortium	Guidance and Advice
Thorax	Primary Research
UKMI – regional centres	Evidence Summaries
US Food and Drug Administration	Safety Alerts; Media and Commentaries

APPENDIX B – Guidance notes for content inclusion by source

These guidance notes detail the protocol for identifying content from the agreed source lists (Appendix A).

Please note, where possible:

- The record needs to link to the original source, not from press releases or other organisation commentaries.
- Link to PDFs directly, **unless specified otherwise.**
- Use NICE Evidence Search to check title and URL format of content.

1. GUIDANCE AND ADVICE

National Institute for Health and Care Excellence (NICE) **http://www.nice.org.uk/**

Check for new guidance at http://www.nice.org.uk/guidance/date

Check for new advice products at http://www.nice.org.uk/about/what-we-do/our-programmes/nice-advice

All Wales Medicines Strategy Group **http://www.awmsg.org/**

Check for new Appraisal Recommendations at:

http://www.awmsg.org/app/report?execution=e1s1

Link to landing page, not PDF.

British National Formulary (BNF) **http://bnf.org/bnf/**

Monthly online updates to BNF content. Highlight important changes

electronic Medicines Compendium (eMC) **www.medicines.org.uk/emc/**

Report on significant SPC changes listed: http://www.medicines.org.uk/EMC/whatsnew.aspx

Pharmaceutical Journal **http://www.pharmaceutical-journal.com/**

Report on significant product updates http://www.pharmaceutical-journal.com/7282.more

Scottish Intercollegiate Guidelines Network (SIGN) **www.sign.ac.uk/**

Updated guidance doesn't get re-listed with new date, therefore review the 'New additions to the site' for new and updated guidance: http://www.sign.ac.uk/new.html

Scottish Medicines Consortium (SMC) **www.scottishmedicines.org.uk/**

New items are listed under the heading 'SMC Advice; Latest Advice' on the left hand side of the page.

Link to landing page, not PDF.

2. SAFETY ALERTS

Central Alerting Service	**https://www.cas.dh.gov.uk/Home.aspx**
Safety alerts and recalls content covering UK drug withdrawals, and patient safety and medical device alerts where relevant to medicines and prescribing	

Medicines and Healthcare products Regulatory Agency (MHRA)	**https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency**
Review Alerts and recalls for drugs and medical devices at http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/index.htm Drug safety updates at https://www.gov.uk/drug-safety-update	

European/International

European Medicines Agency (EMA)	**www.ema.europa.eu/**
Homepage lists tabs for 'Patient Safety'. **NB:** For inclusion of EMA PRAC reports where no MHRA guidance has been published, the UKMI Comment field should include the following statement: "This recommendation has been published by EMA and there is currently no related MHRA guidance available to assess implications for practice in the UK".	

US Food & Drug Administration (US FDA)	**http://www.fda.gov/default.htm**
Review 'Recalls and Safety Alerts' tab for items relevant to UK practice, Including FDA Medwatch	

NB: GOV.UK Warning

When the GOV.UK webpages say that a document has been updated, it might just have been newly added to their site (e.g. moved from the previous organisation website such as HPA or MHRA).

To ensure the document has been updated the publication date within the document needs to be checked rather than the 'last updated' date on the web page.

3. SYSTEMATIC REVIEWS

NIHR Health Technology Assessment programme (HTA)	http://www.journalslibrary.nihr.ac.uk/hta
HTA current volume tab.	

European/International

Canadian Agency for Drugs and Technologies in Health	**www.cadth.ca/**
HTAs listed on http://www.cadth.ca/en/products/health-technology-assessment	
Not to include Rapid Reviews	

4. EVIDENCE SUMMARIES

NICE	**www.nice.org.uk/**
Check for new advice products at http://www.nice.org.uk/about/what-we-do/our-programmes/nice-advice Medicines Evidence Commentaries to be included in the Medicines Awareness Weekly only.	

Drug and Therapeutics Bulletin	**http://dtb.bmj.com/**
Online first and monthly publication	

Midlands Therapeutics Review & Advisory Committee (MTRAC)	**http://centreformedicinesoptimisation.co.uk/mtrac/**
'Latest news' lists all verdict and summary sheets in date order http://centreformedicinesoptimisation.co.uk/mtrac/latest-news	

NIHR	**http://www.nihr.ac.uk/**
Include NIHR Dissemination Centre new Signals: https://discover.dc.nihr.ac.uk/portal/search/signals	

UKMI Medicines Q&A
Include UKMI Medicines Q&A from regional centres by uploading the word document to the CMS record.

5. PRIMARY RESEARCH

Content only to be included where there is open access to full text or abstract, either in the public domain or via NHS ATHENS authentication.

Annals of Internal Medicine	**http://annals.org/**
Online first and current issue linked to from homepage	

Arthritis & Rheumatism	**http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2326-5205**
Current issue	

British Journal of Psychiatry	**http://bjp.rcpsych.org/**
Links to 'Current issue' and 'Latest research' on homepage	

British Medical Journal	**http://www.bmj.com/archive/sevendays**
Current issue and early online	

Circulation	**http://circ.ahajournals.org/**
'Publish ahead of print' and Current Issue linked to from homepage	

Diabetes Care	**http://care.diabetesjournals.org/**
See homepage for current issue and Online Ahead of Print	

European Heart Journal	**http://eurheartj.oxfordjournals.org/**
Homepage lists Current Issue 'Latest'	

Heart	**http://heart.bmj.com/**
Online first and Current issue tabs	

JAMA Internal Medicine	**http://archinte.jamanetwork.com/journal.aspx**
Current issue and Online first tabs on homepage	

JAMA Neurology	**http://archpsyc.jamanetwork.com/journal.aspx**

Current issue and Online first tabs on homepage

JAMA Psychiatry http://archpsyc.jamanetwork.com/journal.aspx

Current issue and Online first tabs on homepage

Journal of the American Medical Association (JAMA) http://jama.jamanetwork.com/journal.aspx

Current issue and Online first tabs on homepage

Journal of Clinical Oncology http://jco.ascopubs.org/

Current issue and Early Release linked to from homepage

Lancet http://www.thelancet.com/journals/lancet/issue/current

Online first and Current issue tabs. Weekly publication

Lancet Diabetes & Endocrinology http://www.thelancet.com/journals/landia/issue/current

Online first and Current issue tabs.

Lancet Infectious Diseases http://www.thelancet.com/journals/landia/issue/current

Online first and Current issue tabs

Lancet Neurology http://www.thelancet.com/journals/landia/issue/current

Online first and Current issue tabs

Lancet Oncology http://www.thelancet.com/journals/landia/issue/current

Online first and Current issue tabs

Lancet Psychiatry http://www.thelancet.com/journals/landia/issue/current

Online first and Current issue tabs

Lancet Respiratory Medicine http://www.thelancet.com/journals/landia/issue/current

Online first and Current issue tabs

New England Journal of Medicine **http://www.nejm.org/**

Weekly publication

Thorax **http://thorax.bmj.com/**

Online first and Current issue tabs

The following news agencies may also highlight key research and trials where the abstract or full text isn't available.
NB: Where possible the record needs to link to original source; news agency can be included under 'related URL' field if appropriate.

BBC Health News **http://www.bbc.co.uk**

Specific Health News webpage: http://www.bbc.co.uk/news/health/

Biospace **www.biospace.com/**

'Top breaking news' listed on homepage, full listings at http://www.biospace.com/news.aspx#topbreaking

Kantar Media Intelligence Health News **http://www.presswatch.com/health/**

New items are listed on homepage.

NB: Copyright issues, report direct from source.

6. POLICY

All Wales Medicines Strategy Group	**http://www.wales.nhs.uk/sites3/home.cfm?orgid=371**
Check for policy updates under tabs	

Department of Health (DH)	**https://www.gov.uk/government/organisations/department-of-health**
Policies at https://www.gov.uk/government/policies?departments%5B%5D=department-of-health	

NHS England	**http://www.england.nhs.uk/**
Updates listed on homepage. News content available at: http://www.england.nhs.uk/category/news/	

Primary Care Commissioning	**www.pcc-cic.org.uk/**
Homepage lists latest reports by date.	

Public Health England	**https://www.gov.uk/government/organisations/public-health-england**
New content listed on homepage.	

NB: GOV.UK Warning

When the GOV.UK webpages say that a document has been updated, it might just have been newly added to their site (e.g. moved from the previous organisation website such as HPA or MHRA).

To ensure the document has been updated the publication date within the document needs to be checked rather than the 'last updated' date on the web page.

7. MEDIA AND COMMENTARIES

Audit Commission	**www.audit-commission.gov.uk**
New items are listed on the homepage, links are under the heading 'Recent Highlights'.	

Care Quality Commission (CQC)	**www.cqc.org.uk/**
Latest news at http://www.cqc.org.uk/content/news	

Central Alerting Service	**https://www.cas.dh.gov.uk/Home.aspx**
Technical drug alerts.	

European Medicines Agency (EMA)	**www.ema.europa.eu/**
Homepage lists 'Latest News', with tabs for 'New Medicines'. Include relevant EU marketing authorization.	

General Pharmaceutical Council (GPC)	**www.pharmacyregulation.org/**
News listed under 'Updates' on homepage or http://www.pharmacyregulation.org/news	

Health and Social Care Information Centre	**http://www.hscic.gov.uk/**
Latest news listed on the homepage.	

The King's Fund	**www.kingsfund.org.uk/**
Latest news listed on homepage	

Medicines and Healthcare products Regulatory Agency (MHRA)	**https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency**
Latest featured on homepage. News feed at: https://www.gov.uk/government/announcements.atom?announcement_filter_option=news-stories&departments%5B%5D=medicines-and-healthcare-products-regulatory-agency	

MIMS	**http://www.mims.co.uk/**
Latest news on homepage	

Monitor	**https://www.gov.uk/government/organisations/monitor**
Latest stories on homepage	

National Audit Office:	**www.nao.org.uk/**
Review latest Publications for health-related items. http://www.nao.org.uk/publications.aspx	

National Institute for Health and Care Excellence (NICE)	**http://www.nice.org.uk/**
Check for updated guidance and quality standards http://www.nice.org.uk/guidance/date Link to update page not landing page, e.g. http://www.nice.org.uk/guidance/qs10/chapter/Update-information.	

National Pharmacy Association	**http://www.npa.co.uk/**
News listed on homepage with full listings at http://www.npa.co.uk/News-Views-Events/News/Publications/?cat=127	

NetDoctor	**www.netdoctor.co.uk/**
'Today's health news' on homepage.	

NHS Choices	**www.nhs.uk/**
Behind the Headlines: http://www.nhs.uk/news/pages/newsindex.aspx	

NHS Confederation	**www.nhsconfed.org/**
'Latest News' listed on homepage.	

NHS Networks	**https://www.networks.nhs.uk/**
News feed listed on homepage	

Pharmaceutical Services Negotiating Committee. **www.psnc.org.uk/**

Latest news listed on homepage, with full archive at http://psnc.org.uk/latest-news/

PharmaTimes **www.pharmatimes.com/**

Daily news at http://www.pharmatimes.com/DailyNews.aspx

Royal Pharmaceutical Society (RPS) **www.rpharms.com/**

'News and updates' listed on homepage and full news listing at http://www.rpharms.com/what-s-happening-/news.asp

US Food & Drug Administration (FDA) **http://www.fda.gov/default.htm**

Review 'What's New Related to Drugs' for items relevant to UK practice, Including FDA Medwatch

http://www.fda.gov/Drugs/NewsEvents/ucm130958.htm

The following news agencies may also highlight media content.
NB: Where possible the record needs to link to original source; news agency can be included under 'related URL' field if appropriate.

BBC Health News **http://www.bbc.co.uk**

Specific Health News webpage: http://www.bbc.co.uk/news/health/

Biospace **www.biospace.com/**

'Top breaking news' listed on homepage, full listings
http://www.biospace.com/news.aspx#topbreaking

e-Health Insider **http://www.ehi.co.uk/**

Headlines are in a box on the front page labeled 'EHI News'. Check current date's items.

Kantar Media Intelligence Health News **http://www.presswatch.com/health/**

Headlines are listed on homepage.

NB: Copyright issues, report direct from source.

APPENDIX C – Information type definitions

9. GUIDANCE AND ADVICE

Type	Description	Example
Guidance	Newly published or updated systematically developed statements to guide decisions about appropriate health and social care to improve individual and population health and wellbeing.	National and accredited guidance producers. Scottish Intercollegiate Guidelines Network guidelines; NICE guidance; Royal College guidance
Drug best practice guidance	Other newly published or updated guidance and recommendations to support the optimal use of medicines.	NICE - Technology Appraisals; All Wales Medicines Strategy Group – Appraisal recommendations; Scottish Medicines Consortium – Advice
Commissioning guides	Commissioning resources to inform local NHS planning and decision-making	NICE guides for commissioners
Drug prescribing	Technical information to support the safe prescribing of medicines.	Significant product licence changes or significant changes to drug monographs. British National Formulary and British National Formulary for Children – prescribing information; electronic Medicines Compendium – Summary of Product Characteristics and Patient Information Leaflets

10. SAFETY ALERTS

Type	Description	Example
Safety alerts	Safety, alerts and recalls content covering patient safety, medical device alerts, drug alerts and drug withdrawals	Medicines and Healthcare products Regulatory Agency; European Medicines Agency; US Food and Drug Administration

11. SYSTEMATIC REVIEWS

Type	Description	Example
Systematic reviews	Selected systematic reviews/ meta-analysis of medicines or lifestyle interventions.	Cochrane Database of Systematic Reviews
Health technology assessments	Assessments determining the clinical and cost effectiveness of a health technology.	National Institute for Health Research Health Technology Assessment

12. EVIDENCE SUMMARIES

Type	Description	Example
Evidence summaries	Summaries of the best available evidence to inform local NHS planning and decision-making.	NICE Medicines and Prescribing Programme Evidence Summaries; Clinical Knowledge Summaries; NIHR Dissemination Centre Signals; UKMI regional evidence summaries e.g. Regional Drug and Therapeutics Centre
Evidence updates	Summaries of newly published selected evidence in relation to accredited guidance. Produced by NICE they highlight where new evidence has been published that might generate a future change in practice.	Evidence Updates from NICE Evidence Resources
Medicines evidence commentaries	A weekly publication from NICE Medicines and Prescribing Centre, providing information on new evidence on medicines currently in use for NHS commissioners, prescribers and prescribing managers.	
Medicines Q&A	UKMI produced evidence-based, quality assured answers to common or unusual medicines related enquires made to local medicines information services.	

13. PRIMARY RESEARCH

Type	Description	Example
Randomised controlled trials	The results of selected Phase 3 and 2 randomised controlled trials into medicines (or lifestyle interventions involving medicines or pharmacy) pertaining to conditions and diseases relevant to UK clinical practice.	Open access to full text or abstract, either in the public domain or via NHS ATHENS authentication.
Other primary research	Articles and reports of newly published or updated primary research which is not a RCT or ongoing or unpublished research.	As above
Ongoing or unpublished research	Ongoing or unpublished research including recruiting trials	As above

14. POLICY

Type	Description	Example
Policy	UK government health policy with a direct relevance to medicines and prescribing.	Department of Health, NHS Primary Care Commissioning, Welsh Assembly Government

15. MEDIA AND COMMENTARIES

Type	Description	Example
Media and commentaries	Press releases and news stories relevant to health care provision in the NHS; organisational draft publications, consultations and commentary; Editorials, selected (non-systematic) reviews and guidelines	NHS Choices Behind the Headlines; National Audit Commission; Care Quality Commission; Health Protection Agency; BBC Health News; Reuters Health

16. OTHER EVIDENCE

Type	Description	Example
Care pathways	Care pathways both describe an ideal model of care for a given condition and provide a way of recording relevant details of what actually happened during the care of a specific individual.	NICE pathways; Department of Health
Drug horizon scanning	Information to support the managed entry of new medicines to the NHS.	National Horizon Scanning Centre – New and emerging Technology briefings; Medicines and Prescribing Centre – New Medicines publications; New Drugs Online – monographs on drugs in clinical development
Drug regulatory and marketing	Information on changes to market authorisations and licensed uses of medicines	Medicines and Healthcare products Regulatory Agency – Regulatory Guidance
Evidence-based management reports	Evidence-based reports or briefings which address key issues in the management of healthcare, public health or social care.	The King's Fund, NHS Improvement
Patient decision aids	Products designed to aid communication and decision making between patients and other service users, and health and social care professionals.	Medicines and Prescribing Centre patient decision aids; NHS Direct patient decision aids,
Drug costs	Information on the economic implications of medicines use.	NICE – costing resources; NHS Economic Evaluation Database – economic evaluations and cost-analyses
Other economic evaluations	Comparative analysis of alternative courses of action in terms of both their costs and their benefits.	NHS Economic Evaluation Database
Drug/medicines management	Systems and processes to support best practice in the use of medicines.	Department of Health – Medicines and Pharmacy content; NICE Medicines Management collection

Type	Description	Example
Audit reports	The outcomes of national audits and equivalent initiatives.	National audits reported by the Information Centre of the Royal Colleges
Effective practice examples	Local, regional or national examples of practice that have been quality assured and found to be effective to deliver evidence-based health or social care or in implementing health and social care policy.	
Implementation support tools	Materials developed specifically to support the uptake and use of evidence in health and social care.	NICE implementation support tools
Learning materials	Selected evidence-based, high quality learning materials.	NICE British Medical Journal learning modules; Medicines and Prescribing Centre learning materials
Quality measures	A measurable element of performance which address process and/or outcomes of health and social care.	NICE quality standards and Quality and Outcomes Framework menu items
Patient information	Publications, aimed at a lay audience.	Patient UK, Medicines for Children, Patient Information Leaflets
Population intelligence	To be applied to statistics, numerical information and data presented in ways to support population health. This type covers both tools and reports. It is suggested that this type may need to be excluded once Public Health England is in place as population intelligence should fall within its remit. No new sources/records should be added with this type.	
Population needs assessments	To be applied to publications which aim to measure the extent and nature of the need of a particular target population in order to make a response to that need.	

APPENDIX D – NICE Evidence Resources Standards of Presentation

To be used in conjunction with NICE Style Guide http://publications.nice.org.uk/nice-style-guide-wg1

1. Information Type field

A record can only have one publication type assigned via using the 'Create New' record template in EpiServer.

See **Appendix C** for Information Type definitions and example of content.

2. Record title field

This is used as the title which appears in the Medicines Awareness Service and in the NHS Evidence search result. This is to be the title of the document or article and should not be edited or prefixed to include, for example, the source name, apart from the following exceptions:

- Truncation of titles which exceed 255 characters (field limit) e.g. primary research titles. Truncate to beginning section of title where possible/comprehensible
- SPC's are preceded by Revised/New Product
- Rewrite sensationalist media headlines to factual description.

The title should be the title of the document being linked to in the Resource URL field. If linking directly to a pdf, then the title of the pdf should be used. If linking to a landing page on a website, then the title of the landing page should be used.

The first letter of the first word only begins in upper case and all other words begin in lower case (with the exception of proper nouns e.g. names of projects, professional bodies such as British Heart Foundation).

In instances where a document has an alternative title (e.g. Equity and Excellence, also known as the White Paper), the alternative title (i.e. "The White Paper") should be put in the description field.

3. Publication date field

Default to today's date, this is the date the document or article was published. If the exact date is not given, use the following convention:

- If only the month and year is given, use 1st of the month
- If only the year is given, use 1st Jan of that year
- If not date is given, e.g. Reuters, use today's date.

For early online bibliographic records use the electronic publication date (which may be ahead of the print version date).

4. Source field

This is a mandatory field and replaces the previous 'Publisher' field. Due to the size of the controlled vocabulary behind this field, it works using Intellisense predictive text – you need to start typing the name of the publisher, and then select the appropriate one from the list that is generated.

For journal articles, the Source is the name of the journal.

For other content, the Source is the name of the organisation e.g. MHRA.

For joint publications this is the lead organisation. Other organisations can be listed in the short summary.

Adding Sources to the controlled vocabularies

You may find that the source name that you are looking for is not in the controlled vocabulary. Please check carefully before adding a new value to avoid bringing duplicates into the lists.

NB: Intellisense list displays a limited number of records at each time, so you may not see the required publisher at first, particularly where the publisher name begins with popular terms e.g. 'Department' or 'Association'.

When adding sources or publishers, the following guidance should be followed:

- The organisation name should be written in full unless the acronym is genuinely the main nomenclature e.g. NSPCC. The main test for whether an organisational acronym is valid is the presence of the acronym in multiple places on the organisation's own website, not just in the URL.
- Don't use ampersands (&); use the word "and" instead.
- Remove any initial "the".
- Take care when assigning the prefix "NHS" to the organisation. Again to decide which is correct, look at the way the organisation refers to itself on its website.
- For journal titles, always give the full title displayed on the website (not an abbreviation), and capitalise the first word and subsequent main words of the title, e.g. Current Opinion in General Surgery.

5. Specialist area field

More than one value can be applied to a record but only to be used where relevant. This field powers the personalisation option on the Medicines Awareness Service, i.e. content assigned to the field will appears in the MAD if the subscriber has chosen that category to display.

(See **Appendix E** for the Speciality list)

6. UKMI Medicines Awareness Weekly relevancy score

Each record is ranked for potential inclusion in the Medicines Awareness Weekly from 1-3.

1 refers to record which are strongly recommended for inclusion in the Medicines Awareness Weekly; 3 to records not considered to be of sufficient importance to merit inclusion. Records of borderline significance are ranked 2.

The fundamental criterion to support the prioritisation of content for the weekly service can be described as the 'Common Sense Test' which asks the question: 'Is it important for a healthcare professional whose practice involves medicines, to be made aware of this piece of information as part of their general current awareness?'.

The following items are to be included in the Medicines Awareness Weekly:

- Safety information, for example Drug Safety Updates, drug withdrawals or licence changes relating to safety.
- NICE products which relate to medicines and prescribing practice.

In addition, other items will be selected for the Medicines Awareness Weekly; these include

- Significant policy changes and developments, for example QOF changes
- Important items relating to medicines, prescribing and evidence-based practice, for example major pieces of research that require, or have the potential to require, changes in practice; issues relating to clarity or availability of research information; review articles relating to matters such as shared decision-making; launches of new medicines
- Information that is relevant to substantial media interest/awareness, for example, key Behind the Headlines articles.

7. Geographical coverage

Use UK / International settings for guidance.

8. Short summary field

Factual description of publication/article limited to 280 characters. This is used as the teaser text in the Medicines Awareness Service, it is not meant to be an appraisal of the publication/article and therefore brevity is important.

The short summary field can be completed by either copying or pasting a snippet of text from a source website, or by creating a summary to describe what the resource is. NB: In order to comply with copyright, it is important that abstracts are not copied and paste from the databases into the field.

Any copied content should be pasted unformatted to ensure the teaser text style displayed in the newsletter is consistent. This text should not include formatting e.g. bold text or bullet points.

The short summary should clearly attribute comments/recommendations/opinions to the author / organisation.

9. UKMI Comment field

This field is to be used for records that are appraised by UKMI i.e. where the abstract or full text document has been reviewed and a short critical appraisal is created by the MIS. This should follow the agreed UKMI Comment Process.

The UKMI Comment can also include related links.

(See **Appendix F** for the UKMI Comment process)

10. Resource link(s)

This field is where the link to the resource is specified. The link should be as specific as possible; ideally the link to the full text PDF. NICE Evidence Search is based on relevance powered by indexing the information available by following the specified URL, therefore a record will perform better if it links to the full text.

To allow indexing of the full text, the link should direct to a document rather than a webpage from which the document file can be obtained.

HTML vs.PDF: Where possible link to the full text PDF, however there are exceptions to the rule, for example:

- Where the PDF link is made up of Javascript which retrieves the document (e.g. the PDFs do not have their own individual URL but sends a request to the website server and returns the PDF) whereas full text HTML link is a permanent URL.
- Where the HTML is open-access and the PDF requires registration.

There are, however, some exceptions from the ingested sources, where the link should go to the landing page, e.g. NICE guidance landing pages which include links to other resources and already have good quality indexing. If a useable URL cannot be obtained the link should direct to the next most relevant page e.g. a landing page.

N.B. under no circumstances should files of any format be downloaded from external sources, stored locally, and subsequently uploaded. This is due to potential issues of copyright infringement, consistency of linking and resource currency. Uploading of files should only take place for UKMI documents e.g. Medicines Q&A where there is no specific URL

If a useable URL cannot be obtained the link should direct to the next most relevant page e.g. a landing page.

For journal articles, where the abstract is freely available on the publisher website, this link should be used. Where the abstract or full text is only available via PubMed the resource URL given should be to the PubMed record.

Where available, the Digital Object Identifier (DOI) should be used in preference to the URL, as DOIs should be more stable.

Additional URLs of related publications/articles can also be added here. They should be used when a document has different formats, or a separate executive summary, or other related documents. The primary resource, which will be indexed by NICE Evidence Search, should be listed first.

APPENDIX E – Specialty Categories

Subscribers of the Medicines Awareness Service: Medicines Awareness Daily will be able to tailor the content they receive by the following categories.

Speciality Area
Policy, Commissioning and Managerial
Allergy and immunology
Anaesthesia and pain
Cancers
Cardiovascular system disorders
Complementary and alternative therapies
Critical care
Diabetes
Ear, nose and throat disorders
Emergency medicine and urgent care
Endocrine system disorders
Eyes and vision
Family planning
Gastrointestinal disorders
Genetics
Haematological disorders
Infection and infectious diseases
Later life
Learning disabilities
Liver disorders
Mental health and illness
Musculo-skeletal disorders
Neurological disorders
Nutritional and metabolic disorders

Obstetrics and gynaecology

Oral and dental health

Paediatric and neonatal medicine

Palliative and End of Life Care

Renal and urologic disorders

Respiratory disorders

Sexual health

Skin disorders

Sports medicine

Stroke

Surgery

Travel Medicine

Vaccination

Wounds and injuries

APPENDIX F - UKMI Comment Process

Aim

The UKMI Comment offers the facility for UKMI to provide a quality-assured, critically appraised, balanced summary of important new evidence about prescribing or the use of a medicine (or group of medicines). They are a prompt response to the publication of important new evidence, so that the NHS has timely access to a quality-assured summary and a balanced commentary. The UKMI comment function may also be used to highlight related links / documents.

The UKMI comment does not reflect the views of NICE and this will be clearly stated on the webpage. However care must be taken when using the UKMI Comment feature to summarise NICE products as these summaries are accessed via a service (Medicines Awareness Daily) provided by and branded NICE.

The UKMI Comment feature should be objective and the content reflects the views of UKMI not the individual Medicines Information Specialist. The opinion or personal judgement of the Medicines Information Specialist should not be included. Previous style rules which allowed the inclusion of opinion by adding this at the end of a summary page prefixed with 'Comment:' are **NOT** to be used.

The UKMI comment feature alerts health professionals to new developments in the evidence base relating to medicines and prescribing. The selected evidence is then summarised and:

- critically reviewed to identify the relative strengths and weaknesses
- placed in the context of the wider evidence base where available
- highlight any potential implications for local decision-making or clinical practice.

The UKMI comment content will be quality assured by the Senior Medicines Information Specialist as part of the MAD quality assurance, to ensure all sections of the document contain statements and conclusions that are fair and balanced. They must, accurately reflect the evidence reviewed and be substantiated by an explicit and appropriate source of evidence. A further check for clarity, grammar, spelling and style is also undertaken to produce a final draft.

<u>For journal content</u> where only the abstract is freely available, the following standardised text should be included in the comment field:

The link will take you to an abstract of the article. NHS staff wishing to obtain a copy of the full text should contact their health care library.

NB. where the journal article is available through open access, omit the standardised text.

The main content of the resource should not be included via this field; the record must link to the appropriate URL or resource.

<u>For related links</u> the following standard text should be used:

"UKMI have identified the following resources which may also be of interest:

- xxx”

For EMA PRAC reports where no MHRA guidance has been published, the UKMI Comment field should include the following statement:

“This recommendation has been published by EMA and there is currently no related MHRA guidance available to assess implications for practice in the UK".

UKMI style and language rules and guidelines [not included]

Appendix E

Medicines Awareness Service: Content prioritisation and publication of the Medicines Awareness Weekly

Standard operating procedure

Version no.	Date	Name	Summary of changes
0.1	25.01.2013	[redacted]	First draft (no appendices)
0.2	18.01.2013	[redacted]	Inclusion of EpiServer process steps and appendices
0.3	21.03.2013	[redacted]	Addition of Appendix C with [redacted]
0.4	28.03.2013	[redacted]	Updated following training session with MPC.
1.1	15/04/13	[redacted]	Updated following implementation of system
1.2	15.04.2013	[redacted]	Inclusion of flowchart
1.3	25/04/13	[redacted]	Update of publishing the MAW, 'ready to send' function.
1.4	20/05/2013	[redacted]	Update of who to send confirmation of completion of each section emails to.
1.5	03.07.2013	[redacted]	Review of SOP.
1.6	19/7/13	[redacted]	Update to process and addition of creating PDF of MEC for ARMs record
1.7	07.08.2013	[redacted]	Re-inclusion of Appendix B, section 2: 2. NICE Evidence Information Services ARMS Record format for Medicines Evidence Commentaries
2.0	25.10.2013	[redacted]	Document review
2.1	18.11.2013	[redacted]	Update IM&T contact email address; accepted v2.0 changes
2.2	17.03.2014	[redacted]	Added note on including MECs in NICE Evidence Search
2.2	04.06.2014	[redacted]	Inserted file pathway for MEC PDF saving
2.3	11.02.2015	[redacted]	Document review and update; clarified steps for editing records in Appendix B
2.4	12.02.2015	[redacted]	Appendix C changed from using ARMS to EpiServer to add MEC
2.5	16.04.2015	[redacted]	Change to Appendix C to avoid inclusion of MEC in MAD
2.6	12.04.2016	[redacted]	Change to Appendix C to include link to reorganized O drive and note to avoid file names with double spaces
2.7	06.02.2017	[redacted];	Added detail about Christmas/NY scheduling. Appendix C changed to use ARMS to add MEC to Evidence Search
2.8	10.05.2017	[redacted]	Updated eIS information specialist contact details
2.9	31.10.2017	Medicines and prescribing team	Various updates to job titles, team names and also to reflect process change.
2.10	02.11.2017	eIS team	Review of Appendix C.
3.0	13.11.2017	[redacted]	Document review completed

Author	[redacted]
Audience	MPT Medicines Awareness Service editors

Purpose

The purpose of this SOP is to assist the NICE medicines and prescribing team in the compilation and delivery of the NICE Medicines Awareness Weekly (MAW) using the EpiServer content management system. This includes guidance notes and criteria for the prioritisation of content to support the delivery of a high quality NICE Medicines Awareness Service – see Appendix A.

Appendix B includes guidance on how to update Medicines Awareness Daily (MAD) record fields that are no longer correct. Changes are only to be made to Title, summary and resources links fields.

Appendix C describes the process involved in uploading the medicines evidence commentary.

Who's who

Role title	Responsibility
MA	Medicines Adviser MPT staff responsible for the prioritisation of content for inclusion in the MAW and quality assurance
Admin	Administrator MPT staff responsible for inserting the medicines evidence commentary (MEC) and the publication of the MAW
APM	Assistant Project Manager MPT staff responsible for checking the MEC in the MAW
AIS	Assistant Information Specialist in the Evidence Information Services team

Resources

- Content strategy
- Medicines Awareness Daily SOP

Process table

[technical process table, not included for publication]

APPENDIX A – Guidance notes for the prioritisation of content in the Medicines Awareness Weekly

1. Medicines Awareness Daily ranking

UKMi is responsible for ranking each Medicines Awareness Daily record for potential inclusion in the Medicines Awareness Weekly. Each record is ranked 1-3.

1	Records which are strongly recommended for inclusion in the Medicines Awareness Weekly
2	Records of borderline significance
3	Records not considered to be of sufficient importance to merit inclusion

2. Medicines Awareness Weekly prioritisation criteria

All Medicines Awareness Daily records are reviewed and assessed by the MPT Medicines Adviser for inclusion in the Medicines Awareness Weekly. Records ranked 1 and 3 are reviewed to agree inclusion or exclusion respectively. A fuller assessment is made of records ranked 2.

The fundamental criterion to support the prioritisation of content for the weekly service can be described as the **'Common Sense Test'** which asks the question:

> 'Is it important for a healthcare professional whose practice involves medicines, to be made aware of this piece of information as part of their general current awareness?'

The following items are to be included in the Medicines Awareness Weekly:

- Safety information, for example Drug Safety Updates, drug withdrawals or licence changes relating to safety.
- NICE products which relate to medicines and prescribing practice.

In addition, other items will be selected for the Medicines Awareness Weekly; these include

- Significant policy changes and developments, for example QOF changes
- Important items relating to medicines, prescribing and evidence-based practice, for example major pieces of research that require, or have the potential to require, changes in practice; issues relating to clarity or availability of research information; review articles relating to matters such as shared decision-making; launches of new medicines

- Information that is relevant to substantial media interest/awareness, for example, key Behind the Headlines articles.

NB: Not all records from the daily service can be included in the weekly service; content is to be restricted to approximately 30 to 40 records. Usually, fewer than 20 records are included each week. Medicines Advisers are not to include 3s if it is a slow week, just to make up numbers, unless they consider them to be higher priority than 3.

Do not include:

- Draft NICE products e.g. for consultation or ACDs or FADs of Technology appraisals. Only final versions should be included
- SPC changes, unless they are very important changes or for a very commonly prescribed drug
- UKMI Q and A documents, unless they include very important changes or a very commonly prescribed drug
- EMA/MHRA New drugs licensed or just got marketing authorization, unless there is a really good reason
- EMA/FDA safety warnings. We usually wait for the subsequent MHRA advice to be reported. However, there might be the occasion where an important EMA safety warning is included if it specifically refers to MHRA advice on the issue

APPENDIX B – Guidance to update MAD record fields that are no longer correct

To update MAD record fields which may no longer contain the correct information, MPT staff should follow the steps below. This appendix also provides details on the standards of presentation for the fields.

Instructions are limited to **Title**, **summary** and **resources links**.

NB: It is not expected that MPT staff will update any other fields.

[technical process, not included for publication]

1. Editing MAD record fields

[technical process, not included for publication]

2. Standards of presentation

Title

The title field is under the 'Information' tab.

This should include the title of the document or article and should not be edited or prefixed to include, for example, the source name. The only exceptions are:

- Truncation of titles which exceed 255 characters (field limit) e.g. primary research titles. Truncate to beginning section of title where possible/comprehensible
- SPC's are preceded by Revised/New Product
- Rewrite sensationalist press and media headlines to factual description.

Short summary

The short summary field is under the 'Article Summary' tab.

Factual description of publication/article is limited to 280 characters. This is approximately 3.5 lines in the Short Summary field and should be written in line with, for example, no new lines or bullet points.

This is used as the teaser text in the Medicines Awareness Service and is not meant to be an appraisal of the publication/article.

Any copied content is to be pasted using 'Paste unformatted' to ensure the teaser text style remains consistent.

The short summary should clearly attribute comments/recommendations/opinions to the author / organisation.

Resource links

[technical process, not included for publication]

NB: The Medicines Awareness Service should link to open access content (abstract or full text) rather than pages which require log-ins.

APPENDIX C - Medicines evidence commentaries

The medicines evidence commentary (MEC) is a weekly publication from MPT providing information on new evidence on medicines currently in use for NHS commissioners, prescribers and prescribing managers.

Prior to publication the MEC is to be prioritised by the team and approved by Publication Executive.

The Administrator is responsible for uploading the MEC to the MAW, following the process steps in the table above, to be published each Monday.

The MEC is included in full text in the Medicines Awareness Weekly and is listed in NICE Evidence Search.

Process for the inclusion of the MEC in NICE Evidence Search

Following publication in the MAW, the Administrator prepares a PDF of the MEC in the NICE Evidence Search MEC template.

[technical process, not included for publication]

APPENDIX D – Troubleshooting

[technical process, not included for publication]

Appendix F

MHRA Drug Safety Updates & NICE Guidance

BACKGROUND

The Medicines and Healthcare products Regulatory Agency (MHRA) produces monthly drug safety updates (DSUs) outlining key safety messages for licensed medicines. In addition, direct healthcare professional communications (DHPCs) are letters delivered directly to healthcare professionals by marketing authorisation holders via the MHRA. These pharmacovigilance communication tools aid education and risk management for healthcare professionals based on emerging data. They may include information on suspension or withdrawal of marketing authorisation of medicines, recalls for safety reasons and important changes to SPCs. These are listed within DSUs.

This proposal outlines criteria for considering;

1. DSUs within guideline development and,
2. Updates through surveillance processes for guidelines, technology appraisals (TAs) and highly specialised technologies guidance (HSTs)

It is important throughout the process to strike a balance between including useful, relevant information and the risk of information overload. Health professionals should consult the BNF, SPC and professional guidance when prescribing and/or administering medicines in correlation with guidance recommendations (e.g. GMC good practice in prescribing and managing medicines and devices).

SUMMARY OF CURRENT PROCESSES

1. **During guideline development**

DSUs are not included as part of the evidence review currently but are expected to be raised by the guideline team if relevant and significant. This could be by NICE staff (e.g. medicines advisors), committee members or during the consultation period. This includes both new guidelines and the update of existing guidelines. The current approach is not consistent in raising relevant DSUs, particularly for guidelines where a medicines advisor is not directly involved. DSUs provide key safety information for relevant medicines-related recommendations, but are at risk of being overlooked with the current process.

2. **Surveillance review of existing guidelines**

Guidelines with a significant number of medicines-related recommendations are reviewed by a medicines advisor and comments returned to the surveillance team for action. There is ambiguity about the actions needed when a DSU is flagged by the medicines advisor. Difficulties also arise where a guideline includes recommendations copied in from TA guidance – this requires a more consistent approach for changes across different types of guidance & pathways.

3. **Proactive review of DSUs for applicability to NICE guidance**

Currently there is not a formal review process. Rather, this is done in an ad-hoc way by a senior member of the surveillance team.

4. **Review of TAs & HSTs**

There is currently no formal review process for MHRA DSUs relevant to technology appraisals. The TA/HST reviews team may be informed of DSUs through various channels (e.g. members of public, other NICE teams) however the timing is variable and relies on a reactive process.

PROPOSED PROCESS

Identifying and prioritising MHRA alerts for action

There is a spreadsheet which is kept in the global drive where all actions and decisions regarding MHRA DSUs should be recorded for future reference. This spreadsheet is accessible to and is the responsibility of all teams involved in the processes described below and can be found here: [redacted]

1. Considering MHRA DSUs during guideline development

- Propose that guidance information services (GIS) incorporate a search of MHRA DSUs for any medicines or medicine classes named in the guideline.
- This would be reported to the development team, and further advice can be sought from the Medicines and Prescribing Team as required, regarding relevance and clinical impact (see appendix A).
- The committee should be presented with relevant DSUs during discussions, so that they can decide on whether the information from the DSU warrants inclusion and how this should be presented (e.g. as part of the recommendation or as a footnote). This additional step will be added to the latest methods manual update.
- The development team should populate the spreadsheet with the decision (and summary of reasons) made by the committee so future reference can be made to this decision.

2. Considering MHRA DSUs during surveillance of guidelines

- MHRA DSUs will be identified by the medicines advisor undertaking the surveillance review of the guideline and will follow the process detailed below in **figure 1**.

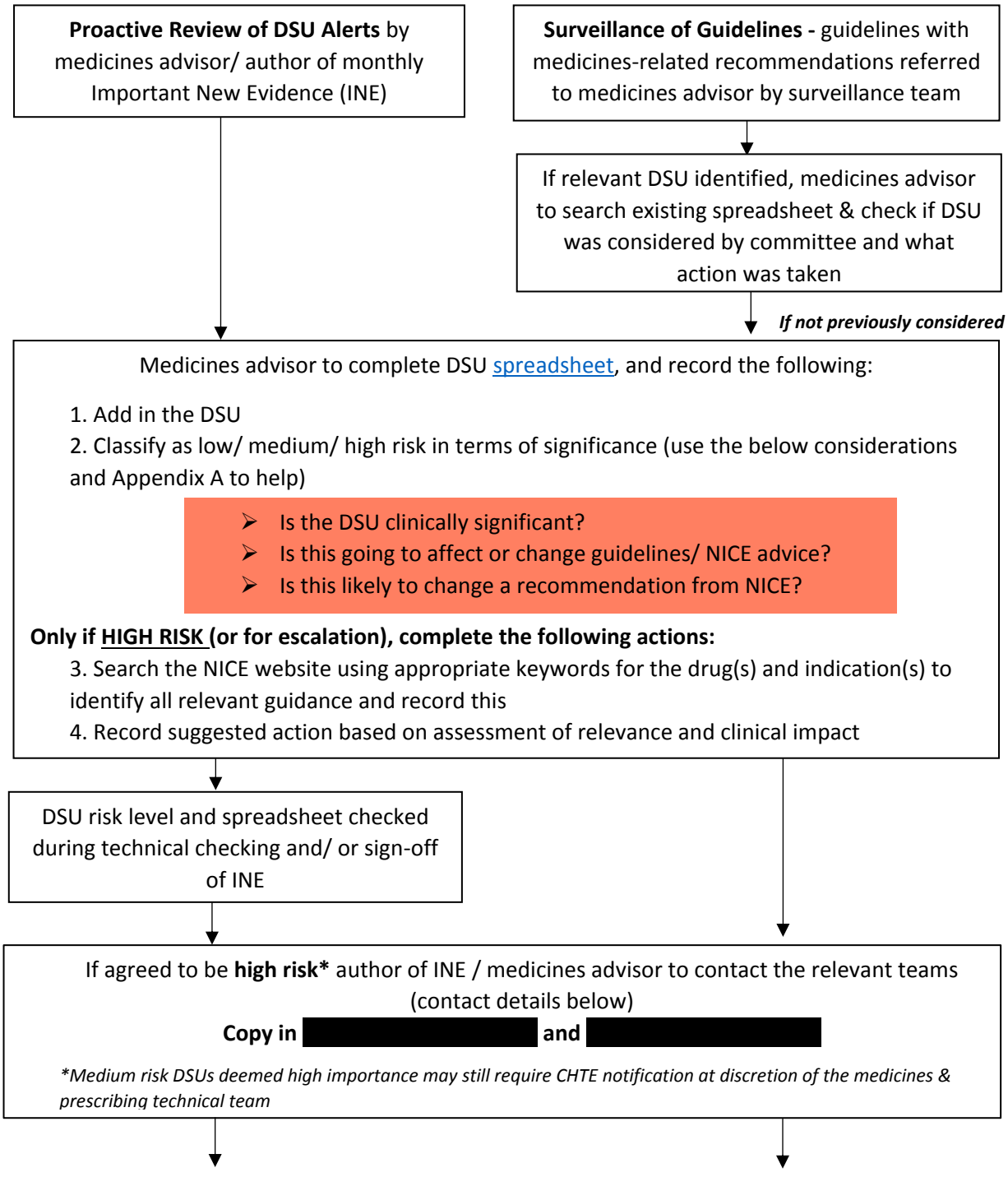
3. Undertaking a proactive review of MHRA DSUs

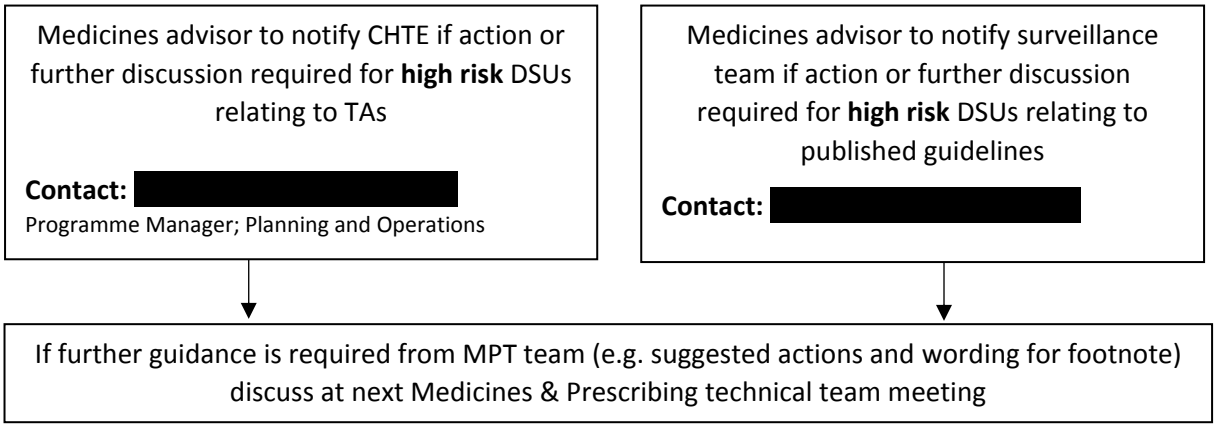
- The Medicines Education Team produce an Important New Evidence (INE) bulletin every month which summarises the DSUs for that time period.
- For each DSU, the medicines advisor will search the NICE website using appropriate keywords for the drug(s) and indication(s) to identify relevant guidance.
- Where DSUs are highlighted that are relevant to TA guidance or guidelines, these should only be notified to the relevant team where the clinical impact assessment suggests **high risk** (see appendix A for advice about this). Contact details for relevant teams are included in **figure 1**.
- For guidelines referred by surveillance for review, where a relevant DSU is identified, the medicine advisor will search the existing spreadsheet. Where a relevant DSU entry does not exist, the DSU spreadsheet should be completed following the process detailed in **figure 1**.

4. Technology Appraisals

- DSUs are usually informed by post-marketing pharmacovigilance and therefore are less likely to be relevant to new TA guidance.
- Safety alerts from DSUs and other data is expected to be submitted by the company and form part of the safety review during TA development.
- Identification of relevant DSUs post TA publication is covered in **figure 1**.

Figure 1: Pathway for proactively reviewing and prioritising MHRA Alerts





A) Resulting actions and communication

Any actions taken **must** be recorded on the DSU spreadsheet. It is the responsibility of all the teams involved to record their actions on this spreadsheet.
The DSU spreadsheet currently has the following actions suggested:

- Nil action
- Insert footnote with link to DSU
- Discuss with surveillance team consultant clinical advisor
- Notify CHTE (TA & HST) reviews team
- Other (explain in comments)

For footnotes to recommendations it is recommended that the wording is kept brief and consists of a link to the DSU and title. For example: *The Medicines and Healthcare products Regulatory Agency (MHRA) issued a Drug Safety Update in January 2015 on Ustekinumab (Stelara): risk of exfoliative dermatitis*

Where clinical guidelines cross-refer to TA recommendations, the current style is for this to be incorporated as a link to the TA. This ensures that the guideline stays up to date in the event that the TA is updated or replaced. If a footnote or other action is required this should be added to the original guidance where possible. For older guidelines where the recommendation/footnotes have been copied rather than provided as a link, discuss further with the editorial team and CHTE (TA & HST) reviews team to ensure a consistent approach where possible.

Actions are recommended by the Medicines and Prescribing Team and completed by the surveillance team (for guidelines) and by the reviews team (for TAs & HSTs) as per the DSU spreadsheet.

During guideline development, actions should be decided by the committee and incorporated into the guideline accordingly.

B) Workload & Capacity

It is anticipated that this workload can be absorbed within current processes and capacity with minimal impact. This will be reviewed after 6 months (by February 2019)

REVIEW OF PROPOSAL

Consultation on this proposal has included:

- Medicines & prescribing team
- Surveillance team

- [redacted](consultant clinical advisor)
- CHTE TA & HST reviews team ([redacted] & [redacted])
- Communications/editorial team ([redacted], [redacted], [redacted])
- Guidance information services, guidance transformation & methods ([redacted], [redacted], [redacted])
- CfG Methods & economics team ([redacted])
- [redacted] (Programme Director, Scientific Affairs)
- MHRA ([redacted] & [redacted])

This process will be reviewed by the clinical fellow, medicines & prescribing team and stakeholders after 6 months (by February 2019) to determine if any amendments are required. The review should address the following questions:

- Is workload for teams reasonable within existing capacity?
- Once the commissioning support programme (CSP) is more established, should this process also cover the CSP publications?
- Are the communication channels and notification via spreadsheet working?
- What are the timelines between identification of DSU and relevant action being take

Appendix A – Clinical Impact Score for MHRA Drug Safety Updates (DSUs)

The following table suggests how DSUs can be scored as low, medium or high risk depending on their impact and clinical severity. Due to the nature and variation in DSUs the table cannot be comprehensive and decisions will be guided by clinical judgement from the medicines & prescribing team.

Impact Score	Suggested Definitions	Examples
1 – Low risk ***(No immediate action required as a result of DSU)***	DSU is a reminder, highlighting a risk well known to clinicians and reflected in product literature (e.g. BNF, SPC)	DSU Feb 2016 – spironolactone & RAS drugs DSU Apr 2016 –skin emollients DSU Nov 2016 - brimonidine
	Lower-risk safety messages which are reflected in product literature. For example: - don't require specific/significant additional screening, counselling, monitoring - low clinical severity (unlikely to cause discontinuation, short term easily treatable adverse effects, not causing significant morbidity/ mortality) - Early signals reported but not yet confirmed	DSU May 2016 – hep B reactivation DSU June 2016 – canagliflozin DSU July 2016 – warfarin
	DSU refers to drug-drug interaction for which clinicians should check in BNF/SPC for advice	DSU June 2016 – miconazole/warfarin DSU July 2016 – citalopram DSU Sept 2016 – levonorgestrel
2 – Medium risk ***(change in practice required)***	Change to how medicine should be prescribed e.g. dosing recommendations or other change in license	DSU Jan 2016 – levonorgestrel DSU Aug 2016 – riociguat DSU Sept 2016 – posaconazole
	Change in counselling or monitoring requirements which may affect choice of therapy and/or have significant resource impact	DSU Feb 2016 – valproate DSU Apr 2016 – SGLT2 inhibitors & MS drugs DSU June 2016 – Nexplanon
	Higher-risk safety messages. For example -high clinical severity (persistent/significant morbidity) requiring specific screening/counselling/monitoring -large population impact -requiring active review of treatment in people already taking the medicine	DSU Jan 2016 – nicorandil
3 - High Risk ***(significant change to treatment pathway)***	Very high risk safety message. For example - Discontinuation or significant change to licensing of medicine e.g. no longer licensed for particular indication or population - Likely to affect position of medicine in treatment pathway - Serious adverse effect linked to: death, life-threatening situation, hospitalisation, persistent/significant morbidity, or congenital anomaly/birth defect	DSU Apr 2016 – meprobomate DSU May 2016 – idelalisib DSU Oct 2016 – retigabine

Appendix G

Surveillance report checklist – NG/CG [XX] [Title of guidance]

Consider these medicines-related questions when reviewing the audit document and evidence review

Guideline recommendations
Does the evidence identified in the surveillance report continue to support the medicines-related recommendations?
Is the new evidence identified through surveillance applicable to current practice? • For example the trial uses a drug that is not available in the UK or is not usually used in practice (may need to ask surveillance team to clarify what is currently used in practice with specialist commentators).
For the medicines-related recommendations do you agree with the decisions made in the surveillance report on whether or not the new evidence is likely to change guideline recommendations
Would a proposed update in one area impact on any other medicines recommendations in the same guideline?
Do you agree with the tables on related NICE guidance in the audit document on what impact updating any medicines recommendations in this guideline may have on medicines recommendations in other related guidance
Safety
For the current medicines related recommendations, follow the NICE Drug safety alert process.
For medicines identified through the surveillance review which are not currently included in the guideline highlight any MHRA drug safety updates that may affect the update decision e.g. if the medicine identified has been withdrawn or if a drug safety update says that the drug should only be used for a specific indication.
Medicines information
Are any new medicines for managing the condition specific to the guideline included in the surveillance review? • Are these new medicines covered by a published TA or a TA in development? • Has this new medicine been covered by a NICE evidence summary? Are there any evidence summaries that may need to be stood down if the guideline is updated?

Have any new medicines launched that should be considered in the surveillance review? • Resources to check for new medicines: Specialist Pharmacy Service – you can check in the new medicines section *(also Prescribing outlook section which lists new drugs in BNF list categories-but don't know if we can get access to this?)*
Check that all relevant TAs have been included in the guideline. • Are the TA recommendations included in the guideline in a consistent format? • Have the TA's been included in the correct section of the guideline?
Check that all medicines recommended in the guideline are either licensed for the indication/dose/route/population they are being recommended for or are appropriately footnoted as being off-label. • Are medicines footnotes in the guideline still applicable?
Complete issues log if necessary: ..\Surveillance issues log.xlsx