The Independent
MEDICINES & MEDICAL DEVICES
Safety Review

The Independent Medicines and Medical Devices Safety Review

Written Evidence

The IMMDS Review has continued to receive a number of emails from individuals and patient groups as part of our regular interaction. These have been carefully considered prior to the writing of the report. In this volume we publish further information the Review has requested following the Call for Evidence and Oral Hearings, and information we were previously unable to publish.

Published July 2020

Contents

Bayer 3
Department for Health and Social Care (DHSC) 13
Ethicon 23
Health & Social Care Department, Scottish Government..... 28
OACS Ireland 41
Sanofi 65

Disclaimer

The statements made and the opinions expressed in response to the Independent Medicines and Medical Devices Safety Review's ('IMMDSR) Call for Evidence and in the video recording of the IMMDSR's oral hearings are those of the authors. They do not purport to reflect the opinions, views or conclusions of the IMMDSR or its members. The statements and opinions made do not imply the expression of any opinion whatsoever on the part of the IMMSDR concerning the truthfulness, veracity, accuracy or legal status of any statements or opinions made and published on the IMMDSR website. Nor does the IMMSDR accept any legal liability arising from any statements or opinions so expressed and published

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

Ms. Valerie Brasse
Review Secretary
The Independent Medicines & Medical Devices Safety Review
Room 3.25b
Shepherd's House
King's College
London SE1 1UL

Dear Ms Brasse

The Independent Medicines & Medical Devices Safety Review –
Re: Primodos

13th December 2018

Mark Wilkinson
Head of Legal and Compliance
Bayer plc
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United Kingdom

email:
mark.wilkinson@bayer.com

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Bayer plc is registered
in England No. 935048

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400 South Oak Way
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We refer to our previous communications concerning the draft Terms of Reference for this review, and the request that we answer certain questions on that aspect of the review which concerns hormone pregnancy tests, set out in the Review Team's email of 16 November 2018. Our answers are enclosed, together with certain historical documents you were seeking. We hope you find this helpful.

We should emphasize that dealing with these questions for any company would be very difficult, given that they largely address events relating to the marketing of a product over 40 years ago. In our case the difficulty is accentuated as Bayer companies never marketed Primodos and their involvement only arises through the acquisition of Schering in 2006. We, therefore, have no first-hand knowledge of the history of the matter and the actions of Schering. The documents on this product held by Schering Chemicals in their old premises were long since destroyed. If the key scientific and medical staff involved in the relevant period at either Schering Chemicals or its parent company are still alive (which we doubt) they are certainly not employees of Bayer plc today.

We are able to provide fairly detailed answers to some of your questions because the UK lawyers for Schering Chemicals at the time of the litigation maintained in their archives a selection of key regulatory documents relating to the history of marketing in the UK. It is these documents that have been used to answer your questions and we should, therefore, note that Bayer plc is not in a position to confirm the completeness or accuracy of the information provided, although we believe that it is likely to be accurate given the historical documents that we have been able to provide.

Against this background and given there is nobody at Bayer plc who could usefully contribute anything on the subject matter of your inquiry, we respectfully decline your offer to attend the oral hearing planned for next year.

Yours sincerely,

Mark Wilkinson

Mark Wilkinson
Head of Legal and Compliance
Bayer plc

Enc

Ms Valerie Brasse
Review Secretary
The Independent Medicines and Medical Devices Safety Review
Room 3.25b
Shepherd's House
King's College
London SE1 1UL

28 January 2019

Mark Wilkinson
Head of Legal & Compliance

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Dear Ms Brasse

Independent Medicines and Medical Devices Safety Review

I refer to our discussion on 9 January 2019 concerning the possible participation of Bayer plc ("Bayer") in the oral hearings that you are planning in relation to the above review. The company holds to its view that it cannot add usefully to either issues of causation (which have now been considered in detail by the competent regulatory authorities), or the historical issues relating to Schering's marketing of Primodos/Duogynon.

In relation to the critical issue of causation, we believe that the decisions of the competent regulatory authorities in the UK and EU, who are charged by the relevant legislature with making complex scientific assessments (and determining whether any scientific issues need to be revisited in the light of new data), must be respected. Bayer and other stakeholders have had the opportunity to make such representations as they believe are appropriate and currently Bayer has nothing to add on this matter. As you know, Bayer co-operated fully with the MHRA and, in order to help inform the CHM Expert Committee's review of the properties of the sex hormones contained in Primodos and other products, Bayer gave the MHRA full access to all the scientific records that it continued to hold relating to norethisterone acetate, ethinylestradiol and combination products that include such active substances. As you are aware, the Expert Group considered all the scientific evidence from all relevant scientific disciplines and concluded that the available evidence does not support the existence of a causal relationship between use of Primodos and adverse outcomes to pregnancy. The MHRA reached the same conclusion in 2014, as has the regulatory authority in Germany (BfArM).

Most recently, the CHMP, which is the Expert Scientific Committee of the European Medicines Agency, has considered the new publication by Brown et al on pre-clinical work in zebrafish. The Safety Working Party of the CHMP has determined that there are so many uncertainties and limitations of the relevant zebrafish data that "the outcome of the study is not relevant for the human situation". It states: "The conclusion, that current non-clinical and clinical data available does not support a signal of teratogenicity of a combination of

orethisterone and ethinylestradiol, remains valid". The CHMP as a whole endorsed that view and, having noted continued use of the relevant sex hormones in other products including oral contraceptives, concluded that the study in zebrafish did not give rise to any new clinical implications. We currently await the assessment by competent authorities of the recently published epidemiological analysis by Heneghan et al. At the MHRA's request, Bayer provided its observations on this study which presents no new data, but simply analyses old epidemiological data differently to the way the MHRA considered such data. We understand that the UK has referred the issue to the CHMP for their Opinion on any potential clinical implications on the human foetus.

When we spoke you specifically asked about our position in relation to compensation schemes that respond to claims that do not require proof of legal liability to compensate. Bayer, of course, sympathises with anyone who suffers from congenital abnormalities, whatever their cause, but for any such compensation arrangements it is normal, at the very least, to require causation to be established. It is not reasonable to expect one person to compensate another unless it is shown that such person is responsible for causing that other person harm.

In relation to your questions concerning the marketing of HPTs in the UK in the 1950s to 1970s, there is nobody at Bayer who has any first-hand knowledge of events at this time. As you are already aware, Bayer did not market Primodos and acquired Schering decades after the marketing of Primodos ceased in the UK. Bayer has provided the factual information you sought where documents were available that enabled us to respond to your questions. We could not do more whether questions relating to events 40 to 60 years ago arise from a statutory or non-statutory inquiry.

You also refer to your broader remit of determining whether there are any "lessons to be learned" from the marketing of HPTs and Primodos in particular that can usefully inform an assessment of how the healthcare system in the UK can respond more effectively to safety concerns about clinical interventions that are raised in the future and you mention the possibility of improvements in the pharmacovigilance system. In short, we do not believe that further examination of events 40 to 60 years ago concerning the marketing of HPTs would provide any useful insights into how the current UK healthcare systems perform and can be improved.

In the days when HPTs were developed and marketed in the UK, a statutory regulatory system was either absent or in the early stages of development. Following a sequence of European Directives and Regulations, today the pharmaceutical industry is the most regulated sector of business. In particular, the monitoring of safety signals in the field of medicinal products is radically different to what it was in the 1950s to 1970s. All aspects of the communication of safety issues to regulators, healthcare professionals and patients themselves are now covered by detailed rules and procedures that relate not only to on-label use of products, but also their off-label use. Since the late 1970s, patient package inserts have normally been required for all products and their contents and readability are controlled by the centralised or national regulatory authorities within the EU. In relation to the obligations of healthcare professionals to discuss with patients the risks and benefits of particular products, including where use off-label is proposed, English law and professional practice are also materially different to what they were in the days when HPTs were marketed. Examining such historic events decades later is not likely to be productive, given the detailed and binding nature of current requirements.

Furthermore, these matters are the subject of harmonised procedures across the EU that seek to ensure that full and objective assessment is made by experts and consistent decisions are adopted by the institutions responsible for protecting public health. These procedures are subject to periodic detailed review centrally. For instance, the pharmacovigilance framework was last reviewed in detail in 2012 and this resulted in changes to procedures to promote further prompt and objective decision making that can result in decisions that are binding on all Member State authorities. We are,

therefore, not aware of any issues that have been raised in connection with the history of marketing of HPTs in the UK that would not now be the subject of detailed and co-ordinated regulatory scrutiny.

We accept, of course, that there are always improvements that can be made to any system, provided the controls are proportionate to the aims of the system. We are aware that the CHM Expert Group has made some suggestions and Bayer has no particular observations to make on those suggestions. In the circumstances, it does not seem appropriate that Bayer gets involved in oral hearings on these issues and is content to leave recommendations concerning the current healthcare system to the careful judgment of your Review Team.

Yours sincerely

Mark Wilkinson

Mark Wilkinson
Head of Legal and Compliance, Bayer plc

The Independent
MEDICINES & MEDICAL DEVICES
Safety Review

FAO: Herr Werner Baumann
Chief Executive Officer
Bayer AG
51368 Leverkusen
Germany

PRIVATE AND CONFIDENTIAL

1 February 2019

Dear Herr Baumann,

My Review, established by the UK Government but independent of it, is examining what has happened in relation to three medical interventions where patients have voiced concern and may have suffered harm. Our role is not only to understand whether and how their concerns were heeded in the past, but also to identify how in the future the healthcare system in the UK can be better at listening to patients and acting on the concerns they raise in order to avoid harm, wherever possible.

I want to listen to the views of all those with an interest in these matters. Our objective is to enhance patient safety and make the healthcare system more responsive to patients. I am sure that is a widely shared objective.

I therefore hope you will agree with me that Bayer, a world leader in the pharmaceutical industry, should contribute its views. Bayer is also a heritage company for Schering AG, the manufacturer of Primodos, a hormone pregnancy test, that is one of the three medical interventions of interest to my Review. Your colleagues have been good enough to contribute information to us in writing. That is most useful and much appreciated. But in my experience there is no substitute for face to face discussion, and we are now at the stage of the Review where we are having those face to face discussions. Our style is not aggressive, inquisitorial or legalistic, as I hope the video recordings of our sessions, available on our website (www.immdsreview.org.uk) demonstrate. We wish to listen and learn. For that reason, I would very much value Bayer's representatives joining us for one of our face to face sessions, as have representatives from other pharmaceutical and device companies. Unfortunately, so far, your colleagues have been unable to commit to doing so, hence I am writing to you now to seek your personal intervention.

I am confident that Bayer would have much of value to contribute to the conversation we wish to have. I very much hope you will feel able to facilitate this.

If you would like to discuss this with me by telephone, I would be happy to do so.

I look forward to your response.

Independent Medicines and Medical Devices Safety Review
Address: Rm 3.25b Shepherd's House, King's College London, London SE1 1UL
Email: reviewteam@kcl.ac.uk | Telephone: 0207 848 6386 | www.IMMDSReview.org.uk

I have sent a copy of this letter to the UK's Secretary of State for Health & Social Care.

Yours sincerely

Baroness Cumberlege CBE DL
Chair
Independent Medicines and Medical Devices Safety Review

cc. The Rt Hon Matthew Hancock MP, Secretary of State for Health & Social Care

RECEIVED BY EMAIL – 22 June 2019

Dear Lady Cumberlege,

I refer to your letter of 1 February 2019 to our Chief Executive Officer, Mr Werner Baumann. Please allow me to reply on his behalf. The delay in making a reply is due to the fact that we first wanted you to receive our responses to your detailed questions, which we have just sent to you.

Although the subject of your request goes back decades, we have done our best to answer factual questions concerning Primodos, where information is available to us from historical papers. We consider, therefore, that Bayer have co-operated to the fullest extent possible to assist your Review. Our response also takes into account the fact that the UK regulatory authorities and the European Medicines Agency have reviewed all of the scientific evidence in detail and have concluded that no causal relationship has been demonstrated between the use of Primodos and congenital malformations.

Bayer would only comment further that, unlike the two other medical interventions with which your Review is concerned, which continue to be marketed, Primodos has not been marketed for many years. It was developed in the 1950s and has not been on the UK market for over forty years. Primodos was not developed or marketed by Bayer but by Schering, who Bayer acquired in 2007. The key scientists and other personnel at Schering in the 1960s and 1970s and involved in these matters are not employed by Bayer and most are probably deceased. In the circumstances, nobody at Bayer is able to speak knowledgeably about the issues you have raised and, therefore, the "face-to-face discussions" you seek could not make any useful contribution to your examination of the history of this matter. Moreover, the entire regulatory system relating to research and marketing of medicinal products has substantially changed and public health and patient interests have been central to those changes. Bayer, therefore, does not believe that any comparison between the system in the 1950s - 1970s and that which prevails today would be useful and, in any event, Bayer is in no better position to address those changes than any other pharmaceutical company.

In the circumstances, we do not believe there would be any benefit to be derived for your Review from a Bayer employee participating in an oral hearing to discuss matters with which he or she had no involvement and has no personal knowledge.

Yours sincerely

Oliver Renner

Head Pharmaceuticals Communication & Health Policy
Bayer AG

From the Permanent Secretary
Sir Chris Wormald

Department of Health & Social Care

39 Victoria Street
London
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permanent.secretary@dh.gsi.gov.uk

Baroness Cumberlege CBE DL
Chair of the Independent Medicines and Medical Devices Safety Review
King's College London, Guys Campus
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SE1 1UL

17 May 2018

Dear Baroness Cumberlege

Independent Medicines and Medical Devices Safety Review

Many thanks for your letter of 1 May. First of all can I thank you for taking on the role as Chair of this important Review and for the work you have already begun in speaking with patient groups.

As a Department, we know that we must support the NHS to do better in the future to ensure that patient voices are bought to the table as systematically and consistently as other voices in the system. We know that some patient groups have worked hard to make their voices heard.

I am aware that you met recently with the Minister for Mental Health and Inequalities to discuss the Review and its progress to date and I know the Minister looks forward to continued engagement.

The Review will be vital in determining both whether the processes pursued to date have been sufficient and satisfactory, and in making recommendations on what should happen in the future to ensure that we do better.

The Department will of course preserve all necessary records as well as be open and transparent in offering evidence of value to the Review. We anticipate that some information may need to be passed to you in confidence, for example where individuals have given personal medical histories. In this case we will need to agree on public reporting of this information, taking into account the Department's responsibilities under GDPR. On other occasions, the volume of evidence may be an

issue for you. In all cases my officials will be happy to work with the Review Team to ensure that you have the appropriate evidence.
I am also happy to meet with you to discuss specific areas of interest, if this would be helpful.

Yours sincerely,

Chris Wormald

SIR CHRIS WORMALD
PERMANENT SECRETARY

SENT BY EMAIL 23rd January 2019

Dear Christopher,

I first wrote to you near the beginning of the Review's work last May to seek your assurance that records and other documentary material containing evidence of value to the Review's work will be preserved and produced on request. Thank you for giving me that assurance in your response of 17th May. In your letter you concluded by saying that officials would be happy to work with the Review team to ensure that we have the appropriate evidence, subject to certain caveats concerning the publication of such evidence and the Department's responsibilities under GDPR. This, too, is much appreciated.

As you will be aware, the Review is currently conducting its oral hearings having received written submissions from patient groups and a wide range of relevant stakeholders, manufacturers, marketing authority holders, clinicians and other health care professionals and NHS public and private sector bodies, following its Call for Evidence last October. You will also be aware that we have yet to receive any written evidence from the Department in response to the questions we raised.

My purpose in writing to you now is to invite you to an oral hearing to represent the Department on Thursday 2nd May and to ask you to confirm that we will receive the written evidence we requested, as given in your earlier assurance, no later than Friday 22nd February.

I look forward to hearing from you.

Yours ever

Julia

Baroness Cumberlege CBE DL
Chair, Independent Medicines and Medical Devices Safety Review

From the Permanent Secretary
Sir Chris Wormald

Department of Health & Social Care

39 Victoria Street
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Baroness Cumberlege
Independent Medicines and Medical Devices Safety Review
King's College, London
Shepherd's House
Room 3.25b
London SE1 1UL

Sent via email to: reviewteam@kcl.ac.uk

14 February 2019

Dear Baroness Cumberlege

Thank you for the work you and your team have put into the Review and the careful work you have done to win the trust of the various stakeholder groups. This is a difficult space to work in and officials tell me that you have taken forward the Review with thoroughness and sensitivity.

I am aware that you have discussed the request you submitted for DHSC evidence with officials, who have explained that as commissioner of the Review we have a responsibility to maintain clear impartiality as the Review goes about its work; we must therefore avoid any appearance of influencing your work or commenting on policy ahead of your recommendations. We are particularly keen to ensure that there is no suggestion of Departmental influence or of our pre-judging the outcome, particularly when you have made your conclusions. It is important for the Department to use your conclusions as the starting-point for further policy thinking – and for that to be clear to the public and stakeholders.

Within the constraints described above, I am keen we continue to do all we can to help you in your work. Officials have therefore prepared the attached document which outlines the key policy/Departmental position. Many of the questions you have asked DHSC concern matters overseen by our health system partners and they are in the best position to answer, with input from us where necessary. I am aware that our system partners have also been submitting evidence to you, and I hope that is helping to answer the questions you have raised. I note in particular the very detailed response supplied by the MHRA. If there are particular further sources of information you would like to access either from the Department or our system partners, officials will assist you in finding the right information. I am aware that you have requested information on archived minutes from meetings relevant to sodium valproate and hormone pregnancy tests, and officials are liaising with our records department and the national archive on that.

From the Permanent Secretary
Sir Chris Wormald

Department of Health & Social Care

I believe officials have explained to you during regular meetings that as a Department we currently do not have a settled policy on the issues you are exploring – indeed that is the very reason you have been asked to look at them. We intend that the outcomes of the review will help us to develop that policy. While I am happy to explain this at an oral hearing, I am not sure this is a good use of the review's time as for the reasons I have outlined, I would need to confine myself largely to stating my anticipation of your conclusions.

Yours sincerely,

Chris Wormald

SIR CHRIS WORMALD
PERMANENT SECRETARY

The Independent
MEDICINES & MEDICAL DEVICES
Safety Review

Sir Chris Wormald
Permanent Secretary
Department of Health and Social Care

28th February 2019

Dear Chris,

Thank you for your letter of 19th February and the enclosed evidence document setting out the key policies/ Departmental position pertinent to the Review. This is much appreciated. Thank you, too, for confirming that officials are liaising with the records office and national archive to provide us with the information we asked for relating to sodium valproate and hormone pregnancy tests.

I am glad we had the opportunity for a brief conversation about the Department's contribution to the Review when we met earlier this week and thank you for your follow-up email.

As you have acknowledged, I and my team have worked to earn the trust of those affected by all three interventions within our scope, and that of the patient groups who campaign so tirelessly on their behalf. It is vital, in maintaining that trust, that we hear from the widest possible range of stakeholders of interest to the Review. We must listen to what they have to say relevant to our terms of reference. The individuals affected, and their families, deserve no less.

As our terms of reference make clear, we are concerned with understanding and commenting on the events of the past and the lessons learned, and with making recommendations that will enable the healthcare system better to respond to safety concerns raised in the future. This may include commenting on the relevant factors that could and should trigger a public inquiry. The Department's position, both now and in the past, having oversight of the whole system and responsibility for the policy that underpins it, is pivotal to that understanding. We must consider and comment on the context in which decisions were made, positions adopted and actions taken or not taken. Hearing from the Department on these matters is vitally important to us, and to those affected.

I fully understand that as the commissioner of the Review you have a responsibility to 'maintain clear impartiality' and must avoid giving rise to 'any appearance of influencing' our work and recommendations. As an independent review, committed to openness and transparency we have made clear that all the evidence we receive in writing or in oral hearings will be published on our website, save for the constraints imposed by GDPR considerations or reasons of confidentiality. We see no reason to treat the evidence given by the Department, whether in writing or in an oral hearing, any differently. The Review's findings and recommendations will be ours and ours alone to make.

This being the case, I am confident we can avoid the perceived conflicts that you refer to in consideration of policy changes going forward. We will continue to look to the Department to

assist us in our work, and to answer all the questions we asked in our Call for Evidence letter looking at both the past and the future, without the caveat you raise.

I look forward to having the opportunity to probe further with you the issue of the Department's accountability, how this has and is being discharged, and other matters relevant to our work at the oral hearing on 2nd May.

Yours ever,

Julia

Broness Cumberlege CBE DL
Chair, Independent Medicines and Medical Devices Safety Review

From the Permanent Secretary
Sir Chris Wormald

Department of Health & Social Care

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Baroness Cumberlege
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Kings College London
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Sent via email to: reviewteam@kcl.ac.uk

8 March 2019

Dear Baroness Cumberlege

Thank you for your letter of 28th February following on my letter of the 19th February.

I am grateful for your understanding of our position, that as commissioner of the Review we have a responsibility to maintain both the reality and the appearance of impartiality. However, I appreciate that it would be helpful for you to hear from us regarding the history of events. On this basis I would be happy to attend one of the Review's oral hearings should you wish to invite me. I would like to be accompanied by William Vineall, Director of the Acute Care and Quality Directorate.

I would be very grateful if you could confirm the time you would like us to attend so we can plan diaries accordingly.

Once again can I thank you for your work on the important issues covered by the Independent Medicines and Medical Devices Safety Review.

Yours sincerely,

Chris Wormald

SIR CHRIS WORMALD
PERMANENT SECRETARY

RECEIVED FROM ETHICON BY EMAIL: 17 December 2018

Dear Valerie,

Thank you for your email of 7th December, kindly responding to the queries raised in our email of 30th November regarding the Independent Medicines and Medical Devices Safety Review and upcoming oral hearings regarding Pelvic mesh products.

In your original email to us of 23rd November (in response to our replies to your Call for Evidence) you set out an invitation to representatives of Ethicon to provide the Review with further assistance by participating in the Review's oral hearing sessions "*to address the topics covered in the Call for Evidence, and relevant to the Review's Terms of Reference*."

You explained that this would provide:

- "*those attending an opportunity to tell the Review team what they think we need to know; and*

- *the Review team an opportunity to ask questions considering the evidence received through the Call for Evidence, and where applicable, in earlier oral hearing sessions*."

Further, "*the Panel may ask questions related to the evidence you have submitted, along with those on any other matters deemed within your field of expertise and relevant to the Review's Terms of Reference*."

Our response to the Call for Evidence was extensive and supported by significant back-up information and documentation. It was prepared with the assistance of a number of individuals with different areas of focus and expertise.

In our email of 30th November we asked for details of "key areas on which the Review Team wish to raise questions, so we can attempt to identify the most suitable individual(s) to attend." You replied "*if there are any specific themes that we wish you to cover we will let you know as soon as possible*." To date we have not been informed of these specific themes.

We also asked if we could be provided in advance with any "*evidence received …where applicable, in earlier oral hearing sessions",* on which you had indicated questions may be put to our representative(s).

Whilst Ethicon wishes to continue to assist with the Review, it's important that we quickly receive the additional information mentioned above so we may identify and confirm availability of the appropriate individuals to respond to the Panel's questions.

Several employees with specialized knowledge across our medical, regulatory, clinical, R&D and other functions provided input on the Call for Evidence. Because it's not practical, nor feasible, to have all of those individuals present at the meeting, our representative(s) will likely be able to address some, but not all, topics that may be raised. Questions outside our representative's area of expertise may be sent to us in writing so we may respond to those as soon as possible.

I trust that this would be a satisfactory process.

I look forward to hearing from you.

With kindest regards

Veronika

The Independent
MEDICINES & MEDICAL DEVICES
Safety Review

FAO: Mr Alex Gorsky
Office of the Chief Executive Officer
One Johnson & Johnson Plaza

PRIVATE AND CONFIDENTIAL

1st February 2019

Dear Mr Gorsky,

My Review, established by the UK Government but independent of it, is examining what has happened in relation to three medical interventions where patients have voiced concern and may have suffered harm. Our role is not only to understand whether and how their concerns were heeded in the past, but also to identify how in the future the healthcare system in the UK can be better at listening to patients and acting on the concerns they raise in order to avoid harm, wherever possible.

I want to listen to the views of all those with an interest in these matters. Our objective is to enhance patient safety and make the healthcare system more responsive to patients. I am sure that is a widely shared objective.

I therefore hope you will agree with me that Johnson & Johnson, and specifically its subsidiary Ethicon, as a leading provider of surgical mesh, should contribute its views. Your colleagues at Ethicon have been good enough to do so in writing, and I know they are willing to provide more information in writing. That is most useful and much appreciated. But in my experience there is no substitute for face to face discussion, and we are now at the stage of the Review where we are having those face to face discussions. Our style is not aggressive, inquisitorial or legalistic, as I hope the video recordings of our sessions, available on our website (www.immdsreview.org.uk) demonstrate. We wish to listen and learn. For that reason, I would very much value Johnson & Johnson or Ethicon representatives joining us for one of our face to face sessions, as have representatives from other pharmaceutical and device companies. Unfortunately, so far, Ethicon colleagues have been unable to commit to doing so, hence I am writing to you now to seek your personal intervention.

I am confident that Johnson & Johnson would have much of value to contribute to the conversation we wish to have. I very much hope you will feel able to facilitate this.

If you would like to discuss this with me by telephone, I would be happy to do so.

I look forward to your response.

Independent Medicines and Medical Devices Safety Review
Address: Rm 3.25b Shepherd's House, King's College London, London SE1 1UL
Email: reviewteam@kcl.ac.uk | Telephone: 0207 848 6386 | www.IMMDSReview.org.uk

I have sent a copy of this letter to the UK's Secretary of State for Health & Social Care.

Yours sincerely

Baroness Cumberlege CBE DL
Chair
Independent Medicines and Medical Devices Safety Review

cc. The Rt Hon Matthew Hancock MP, Secretary of State for Health & Social Care

ETHICON

PART OF THE Johnson & Johnson FAMILY OF COMPANIES

From:
Vladimir Makatsaria
Company Group Chairman (Office E321)
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USA

To:
Baroness Cumberlege CBE DL
Chair, Independent Medicines and Medical Devices Safety Review
Room 3, 25b Shepherd's House,
Kings College London,
London SE1 1UL

And by email c/o reviewteam@kcl.ac.uk

Dear Baroness Cumberlege,

I am replying to the letter we received from you on February 20th addressed to the CEO and Chairman of the Board, Alex Gorsky. As the Company Group Chairman of the Ethicon Inc business I am responding to the letter as the senior leader. I appreciate your personal follow up, and we continue to be open to working with the Independent Medicines and Medical Devices Safety Review Team (IMMDS) to provide information about Ethicon's pelvic mesh products.

Ethicon empathises with all women who suffer with debilitating pelvic conditions, especially those who have experienced treatment complications with or without the use of a pelvic mesh device. At the same time, it is noteworthy that millions of women worldwide with pelvic mesh have seen an improvement in their day-to-day lives.

As you will know from your inquiries to date, many factors can affect the outcome of pelvic surgery, including the risk of complications from surgery, surgical complexity, complications from treatment options and unrelated medical conditions the patient may have.

We wish to continue to assist the enquiry being undertaken by your Review Team, and I have reviewed the detailed exchanges between your Review Team (in particular Dr Valerie Brasse) and our team at Ethicon, together with the detailed written responses and supporting documentation provided by Ethicon to the Review Team on October 24th, 2018, with additional information provided on November 15th, 2018.

ETHICON

PART OF THE Johnson & Johnson FAMILY OF COMPANIES

I can assure you that these detailed responses were the result of considerable effort and collaboration on the part of a team of specialists in different roles at Ethicon, both in the EU and USA, to ensure that we were able to fully address the in-depth questions and requests presented by your Team.

We would welcome any requests for clarification or any additional questions arising from our detailed and thorough responses and - as noted in our previous correspondences - we are fully prepared to provide additional data to support the enquiry as needed.

We received your subsequent request to put forward up to three representatives to attend an oral hearing session to discuss the topics covered in the Call for Evidence, and relevant to the Review's Terms of Reference. Your team has indicated there may be a broad number of areas that the Review team wishes to cover, *"in addition to others that may arise on the day"*. The specific areas you had identified were: *"pre-marketing approvals; post-marketing surveillance; the use of registries; handling adverse event reporting and complaints; priorities for future studies; and alternatives to litigation."*

As we mentioned in our response in January, because the questions may cover a broad range of topics that would fall under the remit of several different sections, individuals, and specialties within Ethicon, representatives would be able to speak only partially to some of the questions. We remain concerned that this discussion would not provide your Review Team with properly informed, complete or in-depth responses.

Accordingly, after careful consideration, our position remains that in order to provide the Review Team with the level of detail and information that it reasonably and properly requires, we invite the Review Team to provide us with the additional questions they may wish to ask and we will address them carefully and respond in writing as soon as possible.

I hope that this detailed response provides you with a clear explanation as to our position and a good level of comfort that we do indeed wish to assist you and your Team. However, if you still wish, we are happy to take up your offer of a discussion by telephone involving one of my UK based colleagues to address any further concerns you may have.

Yours sincerely

Vladimir Makatsaria

Vladimir Makatsaria
Company Group Chairman
ETHICON Inc

Q: In your email of 10 March 2020 you informed us that Ethicon intended to appeal the Australian judgment in Gill v Ethicon Sarl (No 5) [2019] FCA 1905. Please can you confirm if this remains Ethicon's intention? If so please can you confirm whether your intention to appeal is in the public domain and if you would be happy for the IMMDS review to publicly refer to it? If an appeal has commenced, please can you provide further details including the case citation.

The intention to appeal is in the public domain and the IMMDS review may publicly refer to it. The appeal relates to the liability findings (statutory and common law negligence), causation in each of the three lead applicant claims and the orders that two of the lead applicant claims were not barred by limitation statutes. The appeal is of right and leave (i.e. permission) is not required. The notice of grounds of appeal (initiating the appeal process) has been filed and the appeal citation reference is **NSD391/2020 Ethicon Sarl & Ors v Gill & Ors**. Written submissions have not yet been filed and the Appeal Book index has yet to be settled.

Health & Social Care Department, Scottish Government

Provided the following:

- An Investigative Review into the process of establishing, managing and supporting Independent Reviews in Scotland. October 2018 https://www.gov.scot/publications/investigative-review-process-establishing-managing-supporting-independent-reviews-scotland/

- Copies of correspondence between Catherine Calderwood (CMO Scotland) and the MHRA:
    - 31st October 2018 - Letter from CMO to John Wilkinson (MHRA)
    - 15th November 2018 – MHRA response to CMO letter
        - *A copy of this letter was also sent to Jeane Freeman, MSP*
    - 26th November 2018 – CMO response to MHRA letter
    - 13th December 2018 – CMO letter to MHRA, following a phonecall
    - 11th January 2019 – MHRA response to CMO, addressing concerns raised in 26th Nov letter and 13th Dec phone call

Directorate for Chief Medical Officer and Chief Scientist Office
Catherine Calderwood MA Cantab. MBChB FRCOG FRCP Edin, FRCP (Glasgow), FRCS (Ed)
Chief Medical Officer

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year of young people
bliadhna na h-òigridh
2018

John Wilkinson
Director of Devices
MHRA
10 South Colonnade
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E14 4PU
United Kingdom

31 October 2018

Dear John Wilkinson,

Transvaginal mesh implants – patient safety

I would value your view on the recent articles in the BMJ that suggest that shortcomings in existing regulation and post- market surveillance of transvaginal mesh implants have exposed women to avoidable harm.

As a clinician my first duty is to not knowingly cause harm. Avoidance of harm is also a key theme in Realistic Medicine, which as Chief Medical Officer, is my series of annual reports. I recognise that all interventions carry some risk of harm, however, it is important these risks are known and understood otherwise, it is not possible to advise patients and support them in making decisions about their bodies and lives. In this context and in relation to this class of medical devices, is the BMJ correct? In terms of patient safety, is the current system of regulation (including post market surveillance) "fit for purpose"?

I look forward to receiving your considered opinion at the earliest opportunity.

Yours sincerely,

Catherine Calderwood

Catherine Calderwood
Chief Medical Officer

Medicines & Healthcare products Regulatory Agency

MHRA

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15 November 2018

Dear Catherine,

Thank you for your letter of 31 October to John Wilkinson concerning the recent articles in the British Medical Journal (BMJ) about the regulatory system for medical devices. John is currently on leave and has asked me to respond to the concerns that you have raised.

Over recent years we have seen – and will continue to see – ongoing media attention questioning the adequacy of the regulation of medical devices. As you reflect, no medical intervention is without risk and it is entirely reasonable that, when problems do occur with a medical intervention where a device is used, questions are asked about the adequacy of the regulatory system that is in place to minimise the possibility of harm occurring from the use of a medical device.

Regrettably, we have seen relatively little balance in reporting – including in the recent articles in the BMJ – that demonstrates a willingness to properly reflect on the challenges that are faced in the regulation of products which can be extremely complex and where absolute safety cannot be guaranteed. I was particularly frustrated when I read the following statement from the article by Heneghan and Godlee (BMJ, October 2018):

> *Regulatory approval is not a marker of either effectiveness or safety, and this is unlikely to change with the updated EU medical device directives.*

This statement is plainly wrong; at its core, the EU regulatory framework for medical devices requires a manufacturer to demonstrate the safety and performance of their product before it is placed on the market and requires them to monitor its ongoing compliance over its lifespan. Safety is principally about ensuring that the risks posed by a device are minimised as far as possible and any remaining risk is outweighed by the benefits; performance encompasses clinical effectiveness but also other critical technical aspects of a device such as protection for the user/operator of a device or the proper functioning of an alarm feature, for example. The approach taken by the EU to regulate medical devices has been adopted as the basis for the model regulatory framework globally and CE certification provides the foundation for market access to many countries outside the EU.

Taking this into account, the MHRA is of the view that the principles of the current regulatory system are fit for purpose, but we have also been clear about the need to adapt and update the EU legislation in this area to reflect technological developments and ensure that everyone involved – from manufacturers to competent authorities and notified bodies – are acting to the same high standards.

Our evidence to a House of Commons Science and Technology Select Committee Enquiry in 2012 on the regulation of medical implants made clear our assessment of the areas where the regulatory system needs to improve:

- raising the threshold for clinical evidence required for devices – particularly implants – pre-market, reducing the reliance on 'equivalence' and ensuring that appropriate post-market clinical follow-up is undertaken;
- significantly increasing the requirements and scrutiny placed on notified bodies and ensuring that they are applying the increased requirements for clinical evidence consistently;
- supporting traceability of devices through requirements such as Unique Device Identification (UDI) and mandating the provision of implant cards to patients;
- transforming the ability of competent authorities to pool safety data and use the breadth of information available across the EU to inform regulatory actions; and
- significantly increasing the availability of information about devices on the EU market to patients and clinicians.

The MHRA worked extensively during negotiations on the new Medical Device Regulations (MDR) to ensure that our priority areas were reflected in the new legislation and we are clear that this will result in a significant strengthening of the regulatory framework.

It is unfortunate that lengthy negotiations on the MDR mean that it was only adopted in 2017 and comes into force in 2020; recognising that this would be a lengthy process, EU Member States and the Commission have taken a number of actions over the intervening period to ensure the existing legislation is operating as effectively as possible. A key aspect of this was a programme of joint assessments of notified bodies involving inspections by multiple competent authorities and a new team of Commission auditors that has seen the numbers of notified bodies reduce by a third to around 60 since 2012; I anticipate that stricter requirements in the MDR will see numbers fall further over the coming years. Another significant milestone was the publication of new guidance on clinical evaluation in 2016 that clarifies expectations on the need for new high-risk devices to come to market with pre-market clinical data specific to the device in question.

Of course, we face a particular challenge with implantable products since in most cases they are intended to have many years of use inside the human body and there are limitations to what can be studied pre-market, for example in animal models. Equally, it is clearly not feasible to adequately study the absolute long-term safety and performance of implants in patient groups of sufficient size and diversity prior to their being placed on the market. The MDR strengthens the requirements on manufacturers to undertake post-market surveillance of their products but the responsibility for ensuring safe uptake of new implants goes well beyond what can be mandated by a device regulatory system and involves collaboration between manufacturers, those responsible for commissioning care pathways and recommending the use of new products, other regulators and, in particular, the clinical community.

In this context, the MHRA has been supportive of Beyond Compliance, a programme that has been in place since 2013 to support the introduction of hip and knee implants into use in the NHS. The programme was introduced based on a shared view between clinicians, manufacturers and the MHRA that more needed to be done to ensure that adequate information on the safety and performance of these implants is properly collected and rigorously analysed – particularly in the first few years subsequent to CE certification.

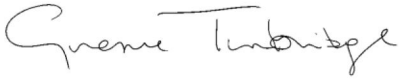
The MHRA would be extremely supportive of considering how a programme such as Beyond Compliance could be replicated in other product areas that would benefit from such an approach, though it is important to note that it was only possible to put this in place because a series of key foundations were in place. These include a mature data collection mechanism (the National Joint Registry), an established system for reviewing post-market performance information on joint replacement implants (the Orthopaedic Data Evaluation Panel) and a cadre of engaged and dedicated clinicians who volunteer their time to support the programme. These aspects largely fall outside of the

MHRA's direct remit and it is clear that any similar programme would require a substantial amount of time and resource to put in place.

Finally, it is worth reflecting that increasing the burden of regulation will mean that potentially life-saving and life-changing technologies will take longer to get to patients, and the increased costs to manufacturers will mean that health systems may have to take difficult decisions not to fund certain technologies. There is a fine balance to be struck between supporting innovation and ensuring appropriate safeguards are in place as ultimately both are in the interests of patients; we should not lose sight of the importance of maintaining proportionate, efficient and effective regulation that will allow us to achieve this.

I hope that this response has provided you with some further explanation and reassurance that the MHRA takes the issues that you raise extremely seriously. I and colleagues from the MHRA would be pleased to meet to discuss this further if you would find that helpful.

Yours sincerely,



Graeme Tunbridge
Group Manager – Devices Regulatory Affairs

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E: [redacted]

Chief Medical Officer Directorate
Chief Medical Officer and Deputy Chief Medical Officer

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Dr Duncan McPherson MBBS FRCA
Clinical Director
Devices
Medicines and Healthcare products Regulatory Agency
[redacted]

26 November 2018

Dear Dr McPherson

Transvaginal mesh implants

I recently received a letter from your colleague Graeme Tunbridge, following my letter to John Wilkinson, regarding recent journal and media reports and concerns raised regarding the regulation of mesh implants.

The letter of response set out a range of work that MHRA states that it has been undertaking. However, I remain concerned about a number of issues, in particular in relation to mesh implants, where I do not yet feel the MHRA has satisfactorily evidenced the safety of these products.

In light of the above, I would welcome some assurance over the steps you have taken to ensure you are satisfied that mesh products, whether transvaginal or hernia, are safe.

I would be grateful if you would set out the process that you have undertaken in order to establish the safety of the products, what evidence you considered as part of that process, and what additional action you have taken in light of the continuing concerns.

In addition there are further areas where I and the Scottish Government have remaining concerns and would appreciate your response on how current appraisal and approval systems can be improved. There are I think a number of questions wher it would be constructive that the MHRA could answer fulsomely.

Understanding and communicating risk: Does MHRA do enough to identify and acknowledge areas of uncertainty and communicate these to users/ recipients?

Should MHRA do more to explain the significance of the CE mark and your "stamp of approval"? Is the recent scrutiny a reflection of a belief by both public and the medical profession that MHRA approval is the same as a safety certificate? Should MHRA identify

known gaps in evidence and knowledge i.e. long term outcomes? Knowledge of "known unknowns'" is relevant in decision making.

Notified Bodies issue CE certification and are crucial in the regulatory process. Is governance adequate and are they fit for purpose?

What is the reasoning for the reduction in number of Notified Bodies? What measures are in place to mitigate the risk of products appearing with unsafe CE certification?

Area for improvement identified by MHRA.

In the letter from Graeme Tunbridge he outlined that in the report on your evidence to a House of Commons Science and Technology Select Committee Enquiry in 2012 on the regulation of medical implants there were a number of points laid out. I am informed that many of these have been rectified in the new EU Medical Device Regulations and I am keen to learn your views of progress and where the NHS in Scotland can support the work. Are these still the areas MHRA identifies for improvement? Are there others? If so, what steps are your now taking as the regulator to take these forward?

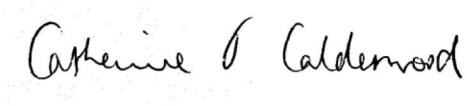
MHRA's relationship with industry: Is it too deferential?

We have previously asked about your relationship with industry in terms of fees and central payment for the work of MHRA. Can you explain the process of reporting adverse events to manufacturers and how you ensure that appropriate action is taken? How open and transparent are the processes involved and what is the supporting legislation? Does this need revision?

Public confidence: How can MHRA restore this?

We are acutely aware of the challenges involved in managing complex systems and the difficulties caused when problems occur. These difficulties are compounded when there is a loss of public confidence. We expect a regulator to function in an open and transparent way and to reflect the needs of the stakeholders, including patients and the public. What are the changes you plan and what is your strategy in order to restore confidence in your organisation?

Yours sincerely,



Catherine Calderwood
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10 South Colonnade
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By email: [redacted]

13 December 2018

Dear John

Thank you and Duncan for taking the time to talk on Tuesday. It was very helpful and I think will help us to move forward. It was also important to voice concerns and share thoughts in what is a challenging time.

During our conversation you mentioned evidence you have submitted to the Independent Medicines and Medical Devices Safety Review (IMMDSR) concerning a meeting MHRA had with the Royal College of Obstetricians and Gynaecologists in 2011. Further, you noted that at the time, there was concern expressed about the safety of vaginal mesh and that measures were proposed to address this. You also spoke of your regret that the necessary actions were not taken and reflected that had they been, then the problems subsequently encountered might have been averted.

You will appreciate that, whilst I am respectful of your candour, I am nevertheless concerned about these disclosures and their implications. From our conversation I understood that this information is not confidential. As a consequence, I would be grateful if, in addition to the written answers to the questions asked already, you could also let me have further details of the relevant evidence, meeting, the actions proposed at the time and what is known about why these were, or were not, acted upon. Finally, sight of your submission to the Cumberledge enquiry would be most helpful.

I am grateful for your assistance with this important matter.

Yours sincerely

Catherine Calderwood

Catherine Calderwood
Chief Medical Officer

Medicines & Healthcare products Regulatory Agency

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11 January 2019

Dear Catherine,

Thank you for your letters of 26 November and 13 December and our phone call on the 11 December 2018.

I have annexed responses to your earlier questions and attached a copy of the Agency's written evidence for the Independent Medicines and Medical Devices Safety Review (also a link to MHRA evidence posted on the Review site is found here).

MHRA recognises some women develop complications related to these surgical procedures, and these can be very significant. Much has been done by MHRA and across the healthcare system to address patient concerns and improve clinical outcomes, and work rightly continues. This is outlined in our evidence to the Review.

I would also like to take this opportunity to clarify the comment in your letter dated 13 December about *regret that the necessary actions were not taken*. My comment was in relation to the actions taken by the healthcare system as a whole in response to the 2011 workshop we hosted and was attended by a range of parties including clinicians (see page 160 of the evidence submitted to the Review). It resulted in a publication in the European Urology Journal. For example, I would have liked to have seen more progress in establishing a registry for mesh and non-mesh urogynaecolgoical procedures (see annex for more details).

As you know, and as highlighted in the Scottish and NHS England reviews and in the 2011 publication, the responsibility for managing and communicating risk in relation to clinical interventions spans the system as a whole with the various parties each having a role.

The significant changes for the European regulatory system will ensure an enhanced level of patient safety by more stringent pre-market and post-market requirements (such as enhanced clinical evidence and post-market clinical follow-up) and increased scrutiny by Notified Bodies. This will be complemented by more structured processes for the introduction of innovative procedures and devices into clinical practice such as Beyond Compliance initiative and the ability to track devices via the Scan4 Safety initiative. The Agency fully supports these developments.

You asked for areas where NHS Scotland could help. I welcome the offer of continued collaboration and would like to suggest the following:

1. Taking a full part in the cross-cutting initiatives
2. Hospitals are not subject to the Medical Device Regulation (MDR), and so MHRA cannot mandate that they use the Unique Device Identifier (UDI). We understand that Scan4Safety has not currently been adopted in Scotland, though there has been significant interest from, and some engagement with the devolved administrations. We encourage NHS Scotland to develop systems like Scan4Safety to ensure that the UDI of a device crosses the 'last mile' into patient's electronic records.
3. Support and action to ensure healthcare professionals embed advice and evidence about devices into their clinical practice.
4. Continue to encourage efforts to ensure healthcare professionals communicate the benefits and risks associated with devices as part of the informed consent process.

   MHRA is aware and appreciative of the important work carried out by the Scottish TV Implants Oversight Group and ongoing delivery of the recommendations contained within the Scottish Independent Review to address points 3 and 4 in particular.

The MHRA continues to stand ready to support you and the healthcare system to ensure the safety of all patients needing treatment.

Yours sincerely

John Wilkinson OBE
Director of Devices

Telephone: [redacted]
E-mail: [redacted]

Annex

Note; Text below cross-references to the Agency's written evidence for the Independent Medicines and Medical Devices Safety Review, see attached.

Assurance on the safety of mesh products

Much work has been undertaken by the Agency to ensure the safety of mesh devices. This is covered in the attached evidence, question 1, and in pages 5-7 for urogynaecological mesh and includes reference to the evidence from a range of sources that we have looked at.

MHRA continue to look at many sources of evidence as part of ongoing market surveillance such as scientific papers, reviews, correspondence from the public, trends from adverse incidents and/or technical and safety data. As you know, no device, medical procedure or intervention is risk free or absolutely "safe", however the standard included in the current Directives and new Medical Device Regulations (MDR), is that risks are reduced as far as possible. Any remaining risks must be acceptable when weighed against the benefits to a patient.

It is clear from some of the reports we have received, that some patients rightly feel these risks were not acceptable for them. The primary role of communicating risk to patients lies with clinicians and MHRA has a role to ensure that manufacturers provide adequate information about their mesh device to clinicians.

Of the main points of the 2011 workshop's conclusions, one point that is still underway is the registry of urogynaecology procedures and devices used. We continue to support the Department of Health and Social Care (DHSC) and NHS England (NHS E) in the development of a registry for procedures which use mesh and non-mesh to treat stress urinary incontinence (SUI) and pelvic organ prolapse (POP) and, like Mr Terence O'Kelly, we have been an active member of the DHSC registry sub-group.

It is outside of our remit to comment on whether the points directed at clinicians have been fully addressed, but we understand steps have been taken by the NHS to address many of these points as found in the Scottish Independent Review and NHS England Mesh Oversight Report.

The new Medical Device Regulations (MDR) gives us the potential to enhance the safe introduction of new technologies and procedures, complimented by the work by the clinical community.

Understanding and communication of risk

The devices specific sections of answers 2 – 14, 20 and 21 address what we do to identify, understand and communicate areas of uncertainty. We aim to improve continuously, and further improvement can be made. For example, there are areas, as you point out, that are known unknowns we would like to understand. This is one of the major areas that we think will be addressed by Unique Device Identifier (UDI) and by the establishment of more sustainable and quality registries that would then allow us to answer some of these questions.

We share your view that the all those within the system should be working towards delivering the conditions of the pause (halt in Scotland) stimulated by Baroness Cumberlege's review. We also strongly support patients getting the best treatment for them and the use of mesh only where evidence supports it as part of an appropriate treatment pathway where strict clinical governance conditions apply as outlined in the NHS high vigilance criteria.

New EU Medical Devices Regulations (MDR)

Implementing the new MDR will improve the current regulatory system, this is covered in our answer to question 33 in the attachment. Our answers to questions 23, 32 and 34 also are relevant. The MDR were passed into UK law in 2017 and have an implementation period that is ongoing now and will fully apply from 26 May 2020.

By 2024, every medical device and in-vitro diagnostic device in Europe, new and old, will have been evaluated so that it conforms with the new MDR or has been removed from the market. There will be no 'grandfathering' of devices into the new MDR standards. In addition, all the extra mechanisms such as EUDAMED (the central European databank of devices) and Unique Device Identifiers (UDI) will have been implemented. For the highest risk devices such as surgical mesh, they will be the first to be required to have UDI by May 2020 and labelled as such by May 2021.

There are other important changes outside the remit of the MHRA that could help strengthen the overall safety of the healthcare system of which devices are only a part. Some of these are addressed in our answer to question 31 and the section on page 35 about improvements to adverse event reporting. We think the National Patient Safety Advisory Committee, Patient Safety Incident Management System (PSIMS) and Healthcare Safety Investigation Branch (HSIB operates in England) are important system-wide improvements.

The MHRA secured extensive improvements to the new MDR that were identified in our submission to the House of Commons Science and Technology Select Committee Enquiry in 2012. What is key now is the successful implementation of it and moving forward on those areas outside of the legislation that we've been working towards such as supporting the delivery of registries.

As with all medical device competent authorities in Europe, the MHRA does not issue a 'stamp of approval' for any medical device. The role of issuing a 'stamp of approval' (i.e., CE mark) is for the manufacturer of the device overseen by a Notified Body where appropriate. It is the role of the Notified Body to ensure that those statements by the manufacturer are accurate and the Agency's role is to supervise this system by auditing the Notified Bodies. It is also the role of manufacturers to ensure their 'stamp of approval' is valid over the lifetime of a device and here MHRA provides more direct scrutiny via our market surveillance and vigilance. We also have enforcement powers to directly restrict or remove a device from use if does not comply with the regulations - response to question 21 provides more information. These powers are reserved for occasions when there is a serious public health threat or if the manufacturer continues to place a non-compliance device on the market.

Governance of Notified Bodies

In 2014, the European Competent Authorities (the MHRA and its equivalents in other EU countries) started a programme of joint audits of Notified Bodies to ensure that they were all operating to consistent pan-European standards. Consequently, some 40 Notified Bodies either withdrew from operation or were suspended. The MDR further raises the standards for Notified Bodies and those remaining in operation will be managed to a consistently higher standard.

You asked about what happened to devices certified by the above 40 Notified Bodies. Manufacturers were required to sign up to a new Notified Body and undergo a reassessment. Any devices that did not gain certification by the new Notified Body were removed from the market.

Further, you should be aware that all devices must undergo regular re-assessment by their Notified Body on a schedule depending on the risk class of the device, at the longest every five years. As already mentioned, all products will need to be certified to the new requirements under the MDR.

Relations with industry

The answers to questions 20 – 22 and on page 114 in our evidence address aspects of MHRA's relationship with industry. To perform our role, it is necessary for us to have a working relationship with industry as we do with healthcare professionals and patient groups.

You were surprised to learn that we have a duty of confidentiality toward device companies that we regulate. In its role as regulator for medical devices, the MHRA works under the Medical Devices Regulations 2002, which implement European Medical Devices Directives 90/385, 93/42 and 98/79. Specifically, Article 15 of Directive 90/385, Article 20 of Directive 93/42 and Article 19 of Directive 98/79 all state:

"Member States shall ensure that all the parties involved in the application of this Directive are bound to observe confidentiality with regard to all information obtained in carrying out their tasks".

In the UK, the EU confidentiality provisions are implemented in law via section 237(2) of the Enterprise Act 2002. This means that information obtained by the MHRA in carrying out its tasks is confidential, and MHRA is therefore obliged to maintain the confidentiality of that information and is prohibited from disclosing it. Furthermore, the Freedom of Information Act places further exemptions on disclosure of information by MHRA.

Having said that, we will release information using a range of communications if there is a need for it and public health benefit. A MHRA Medical Device Alert (MDA) is the main route of safety communication to the health service which we use and are found here.

This is analogous with how other bodies operate such as the General Medical Council (GMC).

Public confidence

During the negotiations for the new regulations, MHRA strongly advocated for greater transparency to be built into the legislation. We did not get all that we asked for. The obligation for manufacturers to publish a summary of clinical performance supporting class III devices such as mesh will be required and available to all. We anticipate during the implementation of MDR transparency will improve, that individual reportable adverse events will be entered into EUDAMED and that this will be available publicly in an anonymised form. We anticipate that improved transparency combined with steps we take to identify and communicate areas of uncertainty/concern will further increase confidence in our role.

1968 TO 2020 Epilim (Valproate) in Ireland

"Why did it all go wrong?"

From 1974 to 2020 there has been collation of Missed Opportunities in the wake of the Monitoring and Prescribing of Epilim (Sodium Valproate) we have chosen not to duplicate what is already written by the UK IMMDS Review Team. However, we have chosen to point out the missed opportunities we have collated in Ireland instead. `

We have asked the HPRA, DOH and Sanofi for some Historical information on Epilim –(Valproate). The HPRA and DOH has passed onto OACS Ireland the 3 licences of Epilim–(Valproate) from 1975 to 1983. OACS also received the PILS/SPC from HPRA 1995/1996 to 2019 the HPRA have stated that there was no PILs before 1995/96 for Epilim-Valproate in Ireland. OACS Ireland recently asked Sanofi for the 1989 to 1995 PIL's and have been denied.

Sodium Valproate (Epilim) is a drug licenced in Ireland for the treatment of epilepsy and bi-polar disorder. Developed in the 1960s, it has been authorised in Ireland since 1975. For many people, Valproate can be an effective drug, in many cases the only effective drug.

It is understood that although Sanofi held a licence for Epilim (Valproate) in Ireland since 1975 and supplied an information leaflet with the product, that same leaflet did not at the time have regulatory approval from the HPRA or its predecessors NDAB. It was simply a marketing insert. In fact, legislation which laid down the requirements for the approval of Epilim (Valproate) in Ireland from the HPRA and its predecessors did not come into effect until January 1994.

OACS Ireland wants an Irish Inquiry ultimately, we are keen to support processes in other jurisdictions that may help achieve this, the voices of families must be heard in Ireland.

"We owe a tremendous amount of gratitude to Epilepsy Ireland for sticking with us and supporting us throughout our journey"

Address: Organisation Anticonvulsant Syndromes Ireland (OACS Ireland). Charity Number (RCN) 20204646. 4 North Brunswick Street Dublin 7 D07RHA8. Postal Box 4. Website: https://oacsireland.com/ Twitter: @oacsIreland Email:office.oacsireland@gmail.com

1968	**NDAB Reports of Side Effects Associated with the Use of Drugs Ireland**	**The Board's own Intensive Monitoring Scheme** indicates that approximately 10% of hospitalized patients experience a side-effect to a drug, either a minor or a serious one. ***This figure is similar to that reported from centres in other*** **countries. Only 1 B hospitals of the over 200 in the country have sent in even one report. Those hospitals from which no reports have come have a total of over 40,000 beds. It is remarkable that no reports have been received from any maternity hospital and from only one children's hospital.** ***(Missed opportunity)***
22 August 1974	**Committee and safety of Medicines UK**	**UK - CSM Minutes 22 August 1974 Minutes** of this meeting state that the committee had considered a request in March of 1974 to remove the monitored release restriction, and that this could be allowed on conditions set out by the Sub-Committee on Toxicity and Clinical Trials. **Additionally, 'Before proceedings 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 [that] on the basis of animal studies, the teratogenic effects of Epilim were of the same order as phenytoin, the Minister agreed to the variation.' In the same meeting, the use of (all) anticonvulsants in pregnancy were further discussed.** The Main Committee agreed that the views of the Sub-Committee on Adverse Reactions should be sought on whether further warnings were required. **Additionally, it was noted that manufacturers of anti-convulsant preparations containing phenytoin and phenobarbitone had been asked (if not already included) to insert the following warning in the data sheets:** '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.'**
1975	**1ST Sodium Valproate License: NDAB January 1975 Department of Health Custom House Dublin 1. Ireland**	**Reckitts (Ireland) Limited, Bluebell, Dublin, 12.** Sirs, I am directed by the Minister for Health to inform you that he has to-day granted your application for an authorisation under the above regulations in accordance with the description and particular conditions in the attached Schedule. The authorisation is valid for a period of 5 years. **GENERAL CONDITIONS** **3.** The holder of the product authorisation shall maintain a record of reports of adverse or unexpected reactions or complaints associated with the use of the product. Such records shall be available for inspection by an officer of the National Drugs Advisory Board, and a copy of all such reports shall be forwarded promptly to the Drugs Division, Department of Health.

		8. The holder of the authorisation shall , on being Informed by the Minister that the medicinal product to which the authorisation relates has been found to give rise to adverse reactions which are unacceptable under the conditions of use ,Immediately withdraw all batches of the product from sale and supply, and, so far as may be practicable. Immediately recall all supplies already sold or distributed. **14. (a) Precautions and Warnings**. In view of its teratogenicity in animals it should not be used in pregnancy unless the physician considers it necessary. **(Missed Opportunity)**
1975	**Published article Symposium on Sodium Valproate held at Nottingham University 23-24th September 1975,**	**1975 Published article Symposium on Sodium Valproate held at Nottingham University 23-24th September 1975, on behalf of Reckitt Labaz. Guy's Hospital Gazette stated:** 'The drug had been released with the warning that it has been shown to be teratogenic in animals. Very few women in this country have been taking this drug during pregnancy, and the data on their offspring is inadequate. Many more women on the continent have presumably had pregnancies while taking the drug, but unfortunately statistical data on the instance of fetal abnormalities were not available. With the memory of thalidomide, few clinicians would be happy to allow their female patients to take sodium valproate at the time of pregnancy risk or during pregnancy until this point has been clarified.'**(Missed Opportunity)**
1978	**NDAB Reports of Side Effects Associated with the Use of Drugs Ireland**	**INTRODUCTION** In order that drugs for therapeutic use **should be given under the best and safest circumstances, it is important that practitioners be aware of potential hazards in their use. To help practitioners, the National Drugs Advisory Board circulates these lists of side effects reported in Ireland at yearly intervals.** The compilation of such a list is limited almost entirely by the interest and concern of doctors and dentists in reporting effects associated with drugs which they have noticed in their patients. **(Missed Opportunity)**
Feb 1978	**FDA (USA); see references Abbott**	**Feb 1978 FDA (USA); see references Abbott were granted a licence to market valproic acid in the US under the brand name Depakene.** The process of licencing had taken 8 years due to requests for further research, including animal studies, dosage studies and controlled trials in humans. **Frustrations with this** process had been aired at a Workshop the previous year, which drew attention to existing international studies (p61), as well as the need for better treatment for patients with epilepsy. **Following a discussion about the difficulty of ascertaining teratogenic effects in a matter of years (highlighting that it took 40 years for the teratogenic effects of phenytoin to be recognised), the workshop also drew attention to the pregnancy forms collected by Reckitt and Colman in the UK (p72). Additionally the workshop papers mention the 'pragmatic' approach of licensing in the UK (p980), which considered available French data, and did not require clinical trials ('the usual procedure for authorization of**

		a non-British Product'), on which basis a limited licence was granted for marketing in hospitals only.(Missed Opportunity)
1980	**Sodium Valproate 2nd License Department of Health Custom House Dublin 1. Valproate Licences** **Reckitts (Ireland) Limited, Bluebell, Dublin 12.**	**Reckitts (Ireland) Limited, Bluebell, Dublin 12. Department of Health Custom House Dublin 1. Valproate Licences.** I am directed by the **Minister for Health** to refer to your application for renewal of the above-mentioned authorisation and to state that the authorisation is here by renewed for a further period of five years' subject to the **"General Conditions" and the "Description and Particular Conditions" set out in the attached schedules**. **3.** The holder of the product authorisation shall maintain a **record of reports of adverse or unexpected reactions or complaints associated with the use of the product**. **Such records shall be available for inspection by an officer of the National Drugs Advisory Board, and a copy of all such reports shall be forwarded promptly to the Drugs Division, Department of Health the Drugs Division, Department of Health.** **14. Precautions and Warnings: 14. In view of its teratogenicity in animals it should not be used in pregnancy unless the physician considers it necessary. (Missed Opportunity)**
March 1980	**Published article Brown et al. - Letter to the Lancet**	**March 1980 Published article Brown et al. - Letter to the Lancet highlighting their concerns about the teratogenicity of valproic acid, arising from their animal data which suggested that valproic acid is a more potent teratogen than phenytoin (a weak human teratogen) and as potent as trimethadione (a powerful human teratogen).** They stated they do not want to 'raise unjustified doubts about a useful drug' and are looking for more information, as published clinical data at that point did not show a relation between valproic acid and human malformations. They ask their colleagues to contact them with any further information on valproic acid use in early pregnancy. **(Missed Opportunity)** See Dalen's 1980
1981	**National Drugs Advisory Board (NDAB)**	**National Drugs Advisory Board (NDAB**) In order **that drugs for therapeutic use should be given under the best and safest circumstances, it is important that practitioners be aware of potential hazards in their use.** To help practitioners**, the National Drugs Advisory Board circulates these lists of side effects reported in Ireland at yearly intervals**. The compilation of such a list is limited almost entirely by the interest and concern of doctors and dentists in reporting effects associated with drugs which they have noticed in their patients. **(Missed Opportunity)**
1981 November 20	**Drug and therapeutics Bulletin.Fortnightly for doctors**	**Drug and therapeutics Bulletin.Fortnightly for doctors from the publishers of Which? ISSN 0012-6543 Volume 19 No. 24.** It has been taken by nearly a million people (70,000 in the UK) and during its first 10 years liver damage and other serious unwanted effects are disturbing. **Teratogenicity 30 pregnancies i n women taking valproate alone a r e known and 24 of them were successful**

	from the publishers of Which? ISSN 0012-6543 Volume 19 No. 24	**and resulted in a normal child; three children were abnormal** and there were three spontaneous abortions. In the few cases with congenital abnormalities in the foetus a causal relationship to valproate is uncertain. **(Missed Opportunity)**
1983	**Department of Health Custom House Dublin 1 Licences.** **Sanofi (UK) Limited, trading in gas: Labaz, Floats Road, Wythenshawe, Manchester M23 9NF, England. Product Authorisation PA 521/1/3. Product Name EPILIM Tablets**	**Department of Health Custom House Dublin 1 Licences. Product Name EPILIM Tablets 200 mg.** Sirs, I am directed by **the Minister for Health** to inform you that he has today granted your application for an authorisation under the above Regulations to market the above-named medicinal product subject to the **"General Conditions" and the "Description and Particular Conditions"** set out in the attached schedules**. This authorisation is valid for a period of 5 years.** Notification that this product authorisation has been granted, has been forwarded to the **Committee for Proprietary Medicinal Products in compliance with article 33 of Council Directive 75/319/EEC of 20th May, .1975.** **Precautions and Warnings 1**. As with other anticonvulsants there is evidence of a **teratogenic effect in animal studies and there have been some reports of congenital abnormalities in offspring of a small number of epileptic patients who were being treated with valproate. There is no clear evidence of a significant association**. However, the **physician should bear this in mind** while also taking into account the effect of seizures during early pregnancy on the mortality and morbidity of the mother and of the foetus. **(Missed Opportunity)**
1983	**BRITISH MEDICAL JOURNAL VOLUME**	**BRITISH MEDICAL JOURNAL VOLUME.** In each of these two cases the mother had taken valproic acid throughout the pregnancy. There are few data on the outcome of pregnancies in which valproic acid was the sole drug taken, **but facial, digital and skeletal abnormalities as well as developmental delay have** been described.2 3. The manufacturers of the drug have collected data on 33 pregnancies in which valproic acid was the sole anticonvulsant **(Labaz, personal communication). These pregnancies resulted in 25 normal babies, four spontaneous abortions, and four infants with congenital malformations (two with meningomyelocoeles, one with syndactyly, and one with a small ventricular septral defect**). **Recently eight participants in the International Clearinghouse for Birth Defects Monitoring Systems reported that valproic acid was associated with neural tube defects in about 1% of fetuses exposed in early pregnancy.** In case 1 dextropropoxyphene as well as valproic acid had been taken at the critical period of differentiation of fetal limb buds. Abnormalities including skeletal and thoracic malformations have been recorded after the use of dextropropoxyphene, usually in combination with other drugs. (**Missed Opportunity)**
1987	**Prognosis in Fetal Valproate Syndrome**	**Prognosis in Fetal Valproate Syndrome** To the Editor: We read with interest the article by Jfiger-Roman et al. (JPEDIATR 1986; 108:997-1004).

		We wonder if the developmental delay and behaviour disturbances in our patient part of fetal valproate syndrome are DiLiberti et al. found developmental delay in two of their seven patients with fetal valproate syndrome. In the first report of a surviving child with the syndrome, **Clay et al. found gross developmental delay, but the diagnosis of neurofibromatosis was made.** Nau et al found slightly retarded psychomotor development without a specific pattern in four of their 12 patients but did not specify whether these were patients receiving valproate alone or with comedication. We, and probably other readers, look forward to news of the long-term growth and developmental follow-up of the patients of patients. (**Missed Opportunity)**
1987	**Prescribing in pregnancy E G BROWN. Sanofi UK Ltd, Manchester M23 9NF**	**Prescribing in pregnancy.** The true incidence of neural tube defect with valproic acid or valproate is probably very low but has not been definitively determined. A spurious accuracy is given to estimates of incidence by quoting them to within half a per cent. **E G BROWN. Sanofi UK Ltd, Manchester M23 9NF. Missed Opportunity**
1989-1990	**Ireland Data Sheet Compendium 1989-90 Women of childbearing age Valproate.** **Sanofi Submission To the UK IMMDS Review Team. 2019.**	**Ireland Data Sheet Compendium 1989-90** **Women of childbearing age:** Some studies have demonstrated an increase in the expected incidence of congenital abnormalities in offspring borne of mothers with epilepsy both untreated and treated. There is evidence of a teratogenic effects with anticonvulsants including Epilim in animals and there has been reports of congenital abnormalities in offspring of a small number of epileptic patients receiving therapy during pregnancy. ***The extent of the relationship is yet uncertain however, the physician should bear in mind as well as taking into account the effect of the seizures during early pregnancy on the mortality and morbidity of the mother and the foetus.*** **Sanofi Submission to the UK Review. An evaluation of the occurrence of specific congenital malformations in women exposed to valproate during the first trimester was first mentioned in the UK Data Sheet submitted in January 1989, approved by the Department of Health and Social Services (DHSS) in April 1989.** **It stated that: *"An increased incidence of congenital abnormalities in off-spring born to mothers with epilepsy both untreated and treated has been demonstrated. There have been reports of foetal 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%".*** **It has been stated to OACS Ireland by the HPRA that there was NO PIL in I989. (Missed Opportunity)**
1989	**REPORT OF THE GENERAL**	**REPORT OF THE GENERAL MEDICAL SERVICES (PAYMENTS) BOARD for the year ended.**

	MEDICAL SERVICES (PAYMENTS) BOARD for the year ended. NDAB	1. 1,570 doctors-and 1,088 pharmacies were registered under the Scheme as at 31st 2. December 1989 and1,568 doctors and 1,099 pharmacies as at 31st December 1988. **3. A total of £158,095,603 was paid to participating doctors and pharmacies in respect of fees, Allowances and medicines for 1989 compared with £137,331,224 for 1988. An amount of £2,038,900 was also paid in superannuation benefits in respect of retired District Medical Officers.** 5. Doctors were paid £50,711,403 in fees and allowances which includes £415,056 paid by (health boards for the year ended 31st December 1989 and £44,600,687 which includes £2,051,996 paid by health boards) for the year ended 31st December 1988 see paragraph 18.1 Page 9). **(Missed Opportunity)**
1989	**PREGNANCY & THE NEO-NATE – PSI**	**PREGNANCY AND THE NEONATE: Pooled data from 13 study groups showed that neural tube defects occurred in 6 of 393 infants exposed to valproic acid compared to 6 of 1718 infants exposed to other antiepileptic agents. It was concluded that this collaborative study confirmed that exposure to valproic acid in the first trimester of pregnancy is causally associated with a considerably increased risk of neural tube defects and that the use of valproic acid during pregnancy should be avoided. - Ref:** D.Lindhoudt and D. Schmidt (letter), Lancet, 1986, 1, 1393. Some further references to congenital abnormalities associated with valproic acid: E. Robert and P. Guibaud (letter), Lancet, 1982, 2, 937; T. Bjerkedal et al. (letter), ibid., 1096 and 1172; O. H. Stanley and T. L. Chambers (letter), ibid., 1282; P. M. Jeavons (letter), ibid; E. Castilla (letter) ibid., 1983, 2, 683; E. Robert and F. Rosa (letter), ibid., 1142; P. Mastroiacovo et al, (letter), ibid., 1499; D. Lindhout and H. Meinardi (letter), ibid., 1984, 2, 396; E. Robert et al (letter), ibid., 1392; J. H. DiLiberti et al., Am. J. med. Genet., 1984, 19, 473; A.S. Garden et al., Can. med, Ass. J., 1985, 132, 933. **(Missed Opportunity)**
1989	**VALPROATE, SPINA BIFIDA, AND BIRTH DEFECT REGISTRIES. Lancet** **Dr HUGH STAUNTON. Ireland**	**VALPROATE, SPINA BIFIDA, AND BIRTH DEFECT REGISTRIES. Richmond Institute for Neurology and Neurosurgery, St Laurence's (Richmond) Hospital, Dublin 7, Ireland. HUGH STAUNTON.** Sir, Your Dec 17 editorial (p 1404) refers to the question of prospective studies. Before Robert and Guibaud, I had drawn attention to the possible connection between valproate and birth defects. **2. A review of the data revealed that of 31 mothers taking valproate alone, there were 24 normal babies, 3 spontaneous abortions, and 3 livebirths with congenital abnormalities, including a dysmorphic female with multiple severe abnormalities, spina bifida, and significant immaturity.** Since then, I have rarely prescribed this drug in pregnancy. Given the reports, what woman will freely enter a prospective trial? **(Missed Opportunity)**

1989	**BIRTH DEFECT REGISTRIES Lancet**	**BIRTH DEFECT REGISTRIES. SIR**, -Your editorial (Dec 17, p 1404) on valproate implicitly questions the utility of birth defect registries for investigating potential teratogens is. **Such registries have been proliferating, and they are demanding in terms of time and money. Given their apparent lack of productivity in detecting epidemics of congenital defects, do we really need them?** **I suggest that we do, for two principal reasons. First, congenital defect monitoring fulfils an important public health function, even when results are consistently negative.** **…Second, the mere existence of registries may deter teratogenic incidents in the same way that speed-traps act as a deterrent on our roads. If there is a reasonable probability of environmental or pharmacological teratogens being detected, potential offenders (including the pharmaceutical industry) are more likely to behave responsibly.** Medical Protection Society, 50 Hallam Street, London W1N 6DE R. N. PALMER. **(Missed Opportunity)**
1991	**NATIONAL DRUGS FORMULARY** **NDAB**	**Appendix F: Reporting of Adverse Drug Reactions** **AII adverse drug reactions should be reported on the supplied form to the Medical Director National Drugs Advisory Board 63-64 Adelaide Road. Dublin 2. Telephone 764971/7.** This Index can be used as a cross-reference for the identification of the proprietary and non-proprietary products covered by the Formulary. In order to encourage the use of non-proprietary (i.e. generic) names in prescribing. all non-proprietary names in the index arc in bold type. **Proprietary names are included for information and convenience. Where a non-proprietary name is given in the Index it is followed by the names of ·the available proprietary products. Where a proprietary name is given. It is followed by the appropriate non-proprietary name. (Epilim -Valproate). (Missed Opportunity).**
1992	**Congenital Anomalies in the Offspring of Epileptic Mothers**	**Congenital Anomalies in the Offspring of Epileptic Mothers***Yoshibumi NAKANE' and Sunao KANEK02. Department of Neuropsychiatry, Nagasaki University School of Medicine, 1-12-4. Sakamoto, Nagasaki 852, Japan and 'Department of Neuropsychiatry, Hirosaki University School of Medicine, 5 Zaifu-cho, Hirosaki, Aomori 036, Japan. **4) Recommendations Concerning AED Intake during Pregnancy.** Based on the research and **studies reported in this paper, the Commission on Genetics, Pregnancy, and the Child of the International League Against Epilepsy 1989, made the following recommendation: Epileptic women, when they become pregnant, should be informed that there is a risk of major malformations and minor anomalies related to their family history, and the type and severity of their epilepsy**.

		Further, they should be informed that fetuses and neonates may have developmental disorders, and that they might experience various types of convulsion. In particular, VPA, which has the risk of inducing neural tube defects, should be replaced by other AEDs. Heart defects and facial clefts can sometimes result from the use of AEDs, and so ultra-sound examination is recommended to find out if such malformations exist. In the treatment of epilepsy, a single AED regime with the lowest possible dosage is the most desirable medication. Finally, blood concentration of AED should be continuously monitored. **(Missed Opportunity).**
1994	**Guy's Hospital, London. Dr O'Brien.**	**Guy's Hospital, London Epilepsy and pregnancy/ MD O'Brien, S Gilmour-White. SEI 9RT MD O'Brien,) Physician for Nemours diseases. S Gilmour-White, pharmacist Correspondence to Dr O'Brien. COMMON ABNORMALITIES** The commonest malformations are **cleft lip and palate and congenital heart disease, usually septal defects. These abnormalities may be caused by all the major antiepileptic drugs, especially when used in combination. (Missed Opportunity)**
1992	**THE NATIONAL DRUGS ADVISORY BOARD. Consolidated Annual Reports 1991-94**	**THE NATIONAL DRUGS ADVISORY BOARD** **(e)** to advise the Minister and others concerned as to the precautions or restrictions, if any, subject to which drugs may be marketed or continued in use in the State. **(e) if requested by the Minister, to advise on the licensing of the manufacture, importation, distribution and sale of drugs, on the standards of manufacturing practice (including quality control) of manufacturers of drugs and on the certification for export purposes or for any other purposes of drugs.** **(f) if requested by the Minister and subject to such conditions as he may approve, to arrange for the collection and dissemination of information in respect of drugs, their pharmacological classification and therapeutic efficacy and in respect of economies in prescribing. (Missed Opportunity)**
1994	**National Drugs Advisory Board annual report and accounts.**	**1994 National Drugs Advisory Board annual report and accounts. The National Drugs Advisory Board.** **Chairman's Report** **In 1991 the decision was taken that the Board should become responsible for licensing human medicines and that it should be self-financing. On 27th June 1995, the Irish Medicines Board Bill was introduced by the Minister for Health to provide for the establishment of the successor Body to the NDAB to be known as the Irish Medicines Board and the formal existence of the NDAB ended on December 31st, 1995. (Missed Opportunity)**
1994	**All Board**	**NATIONAL DRUGS ADVISORY BOARD**

	ANNUAL REPORT 1994. **Consolidated Annual Reports 1991 - 1994** **1. Introduction.** **2.Annual Report 1991.** **3.Annual Report 1992**	**4. Annual Report 1993.I. GENERAL MATTERS** **2.HUMAN MEDICINES 2.1 Introduction** **The Board continues to receive a large number of spontaneously reported side effects from healthcare professionals. These are recorded. Evaluated and used to update prescribing recommendations where necessary**. The anonymous data is then integrated into the WHO database where it provides a valuable international resource. Post-marketing surveillance activities remain the cornerstone of our information source in monitoring the safety of medicines in Ireland and we would like to record our appreciation of all those who participate in our spontaneous reporting scheme. **2.4 Pharmacovigilance 2.4.1 Adverse Drug Reactions** The Board received 1054 reports of adverse drug reactions during the year**. Pharmaceutical companies provided the largest proportion (38.3%) followed by general practitioners (31.4%), hospital doctors (12%), community pharmacists (6.7%,), hospital monitoring studies (6%) and nurses (2.3%).** There were 35 deaths recorded in association with drug use. Of these, 28 were related to the primary illness, 1 was associated with drug overdose and 1 was associated with suspected teratogenic effects (cardiac) in a neonate. In the remainder is was not possible to assign an aetiology. There were 13 reports of drug interactions. Further details of the above will be published in a separate report. **(Missed Opportunity)**
1996	**NDAB Guidelines MANAGEMENT OF EPILEPSY IN GENERAL, Practice**	**NDAB Guidelines MANAGEMENT OF EPILEPSY IN GENERAL, PRACTICE. Ireland Guidelines MANAGEMENT OF EPILEPSY IN GENERAL PRACTICE Ireland** Overall, children of epileptic mothers taking anticonvulsants **have roughly twice as many significant malformations (6%) as children of mothers in the population as a whole.**' There appears to be no data documenting an increase in risk to the foetus due to seizures**, compared with teratogenic defects occurring in patients taking anticonvulsant medication.** **(Dr N Callaghan, personal communication). Some women with epilepsy may become pregnant unexpectedly while taking oral contraceptives if they are also taking enzyme inducing anticonvulsants, eg phenytoin. This is more likely to happen if a low dose contraceptive pill is used but may also occur with the 50-microgram oestrogen contraceptive. Women must be advised of this risk and use either an alternative method of contraception or change their anticonvulsant if they do not wish to become pregnant. There is an association between sodium valproate and neural tube defects. Recently reports of spina bifida in infants of mothers who used carbamazepine in pregnancy have appeared, making the choice of an appropriate anticonvulsant in pregnancy a very difficult one.**

		Monotherapy with carbamazepine is probably the best choice. Neonatal withdrawal symptoms and signs: may appear at this time in the children of mothers who have been on anticonvulsants during pregnancy. Expectant supervision is usually adequate. If tremulousness or seizures develop,3 to.5 mg/kg/day of phenobarbitone may be given. **Breast feeding:** MOTHERS MAY BREAST FEED Mothers taking anticonvulsant drugs may safely breast feed their children. **(Missed Opportunity)**
1998	**NDAB Report Ireland Women's health: family planning an information booklet**	**Women's health: Family planning an information booklet. Report Ireland Women's health:** Family planning an information booklet for health care professionals **by Dr Yvonne Rafter** Some drugs such as anticonvulsants for example, are associated with a higher incidence of congenital abnormalities. This should be discussed with the patient. Most patients are advised to continue with their medication especially those with asthma. Patients often discontinue their medication with a resultant deterioration in the medical condition**. (Missed Opportunity)**
2001/ 2007	**Irish Epilepsy and Pregnancy Register.**	**Irish Epilepsy and Pregnancy Register** Data Collection Type. National data collections of health and social care in Ireland. Organisation Beaumont Hospital Epilepsy Research Group, Royal College of Surgeons in Ireland Web address **http://www.epilepsypregnancyregister.ie/** Year established: 2001. 2007 — amalgamated with UK epilepsy and pregnancy register. **(Missed Opportunity)**
2005	**Management of epilepsy in women M D O'Brien, S K Gilmour-White.**	**Management of epilepsy in women. M D O'Brien, S K Gilmour-White. Valproate exposure and developmental delay** There is some evidence that children exposed to valproate in utero shows an increased incidence of developmental delay. Gaily et al found no effect from in utero exposure to carbamazepine, but a significantly reduced verbal IQ (VIQ) in children exposed to polytherapy with valproate. An independent effect from valproate could not be determined because the results were confounded by low maternal education and polytherapy. Adab et. al showed that children exposed to valproate monotherapy had significantly lower VIQ scores when compared with children exposed to carbamazepine and to phenytoin monotherapy, and there was some evidence of a dose effect. **The use of valproate should therefore be avoided in women of childbearing age, particularly in the obese, especially in obese adolescents, and in those women with menstrual irregularity. Consider withdrawal of valproate in women who develop obesity and or menstrual irregularity while on valproate. (Missed Opportunity)**
2006	**Afssaps** **Pregnancy and breast feeding.**	**Decision: 4.6. Pregnancy and breast feeding.** **On the basis of currently available data, the use of sodium valproate is not recommended during pregnancy and for women of childbearing age in absence of effective contraception.**

	FRANCE	**In humans, sodium valproate causes a risk of fetal malformation three to four times higher than for the general population which is of 3%. The most common malformations are abnormalities causing faulty neural tube closure (around 2 to 3%), facial dysmorphia, oral-facial clefts, craniostenoses, cardiac malformations, kidney and urogenital malformations, and malformations of the limbs.** **Dosages higher than 1000mg/j and the association with other anti-convulsant medication are important risk factors giving rise to malformations.** **Current epidemiological data have not shown diminished IQ levels among children exposed in utero to sodium valproate. However, a slight decrease in verbal capacities and/ or increase recourse to speech therapy and to special needs support have been observed among these children. Moreover, some isolated cases of autism and similar disorders have been reported among children exposed in utero to sodium valproate.** **Additional research is required to confirm or invalidate these results as a whole. If pregnancy is being planned: All measures / steps will be taken to consider recourse to other therapies in preparation of / ahead of this pregnancy. Missed Opportunity**
2005	**Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register.**	**Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register.** J Morrow, A Russell, E Guthrie, L Parsons, I Robertson, R Waddell, B Irwin, R C McGivern, P J Morrison, and J Craig. **Data analysis** Outcomes were classified by one of us (PM) into those without birth defects, those with MCMs, and those with other defects (minor defects, chromosomal disorders, and single gene defects). **For each of these categories, outcomes were further subdivided into live births and pregnancy losses (spontaneous pregnancy losses or induced abortions). The results were also stratified by whether exposure was part of a monotherapy or a polytherapy regimen.** An MCM was defined as an abnormality of an essential embryonic structure requiring significant treatment and present at birth or discovered during the first six weeks of life. Disorders not conforming to this definition were assigned as minor malformations based on the definitions and lists of disorders in the EUROCAT registry. **Developmental delay and cases of fetal anticonvulsant syndrome—where there was a combination of dysmorphic features but no major**

		defects as defined above—were coded as minor structural malformations, although they are significant defects in themselves. (Missed Opportunity)
2008	**ANTIEPILEPTIC DRUG TERATOGENESIS: WHAT ARE THE RISKS FOR CONGENITAL MALFORMATIONS AND ADVERSE COGNITIVE OUTCOMES. Cynthia L Harden 1**	**ANTIEPILEPTIC DRUG TERATOGENESIS: WHAT ARE THE RISKS FOR CONGENITAL MALFORMATIONS AND ADVERSE COGNITIVE OUTCOMES.** The assessment for cognitive teratogenesis is quite different than for MCMs. The studies must be blinded or masked due to the relative subjectivity of the outcome. Confounders, such as social environment and maternal IQ, must be accounted for in the analysis. Further, the intellectual assessment of young children begins to be reliable only after the age of 2 years, therefore the studies must be long term in design. **Another consideration is the timing of exposure for cognitive versus structural teratogenesis. MCMs develop within the first 13 weeks of gestation; however, there is evidence that perhaps later exposure during pregnancy has a impact on cognitive outcomes (Reinisch et al., 1995).** Given these considerations, there are several well-performed studies that shed light on this important concern for WWE. Firstly, similar to the risks for MCMs, several studies indicate that AED polytherapy exposure during pregnancy poses an increased risk for adverse cognitive outcome compared to monotherapy **(Gaily et al., 2004; Koch et al., 1999; Lo¨sche et al., 1994).(Missed Opportunity)**
2009	**CORK AND KERRY EUROCAT Special Report Volume 3, Issue 1, 2010. EUROCAT**	**CORK AND KERRY EUROCAT Special Report Volume 3, Issue 1, 2010. EUROCAT Special Report:** The Status of Health in the European Union: **Congenital Malformations (June 2009)** The study also compared the use of valproic acid with the use of other antiepileptic drugs and found similar results, suggesting that valproic acid has higher risks associated with birth defects compared to other antiepileptic drugs. Although the relative risks of several birth defects were increased after 1st trimester exposure of valproic acid, it should be recognised that the risks of these specific birth defects are still low, ranging from 1 to 7 per 1,000 exposed pregnancies. **(Missed Opportunity)**
2011	**Rare but Real - The Effects of Sodium Valproate in Pregnancy**	**Rare but Real -The Effects of Sodium Valproate in Pregnancy. The mainstream practice of medicine needs to be strong in the face of ill-defined half-baked observation, populist rumour, medical faddism and profit driven propaganda**. Equally, practice must not be sclerotic or dismissive of uncomfortable findings, even if individually rare. **Optimal practice is best served by mutual respect between different subspecialties and an awareness of the difficulties that attend consolidating rare events in medicine by the rules of statistical analysis. Fetal Valproate syndrome is a good example of the convoluted course which a rare condition may take to emerge into mainstream acceptance? It behoves all**

		who prescribe Valproate to be aware of potential offspring consequences for female patients in the reproductive age range. Recent evidence suggests that the focus in respect of latter day prescribing of Sodium Valproate may have shifted from Neurologists towards Psychiatric practice, where its use as a mood stabiliser makes it the most commonly prescribed agent for young women in one recent study. An unresolved issue remains in respect of embracing the concerns of those in medicine whose expertise in rare disorders places them outside the mainstream voice and therefore, at risk of being unheard**. The question is whether it should take 30 years for the teratogenic effects of a commonly prescribed drug to be accepted and mainstream practice modified. Department of Clinical Genetics, Our Lady's Children's Hospital, Crumlin, Dublin 12. Dr William Reardon. (Missed Opportunity).**
2011	**Irish medical journal Towards the development of integrated epilepsy services: an audit of documented epilepsy care. Documentation evidence of integrated epilepsy care.**	**Towards the development of integrated epilepsy services: an audit of documented epilepsy care. Documentation evidence of integrated epilepsy care. Over 70% of patients had not received a neurology review within the past 2 years nor was there evidence of their care being co-managed with specialist epilepsy services. Information specific to patient compliance with advised treatment regime and/or life-style modifications was infrequently documented.** **(Table 2). Documentation of Anti-Epileptic Drugs (AEDs) The majority of patients (93%) were taking at least one, while 145 (43%) were taking two or more AEDs. The most commonly prescribed AEDs included Carbamazepine, Valproate Chrono, Valproate and Lamotrigine. Documentation relating to Buccal Midazolam use and/or information regarding prior AED efficacy was rarely available. 82 (22%) patients were women of childbearing age (16-50 years) with 33 (44%) currently taking Valproate. Information specific to epilepsy care during pregnancy was unavailable (66%) as was evidence of integrated neurology review (76%) (Missed Opportunity)**
2013	**The Awareness**	Karen Keely continues to raise awareness and hopes that she will find that person and /or organisation that will believe in her.
2014	**FACS FOURM Setting up of the FACS Forum Ireland**	**FACS Forum Ireland was formed as the result of campaigning by Ms Karen Keely.** Karen Keely has contended for many years that advice given to patients by both industry and the health services in Ireland have been inadequate, despite the availability of extensive research on birth defects and sodium valproate. The FACS Forum was established as a result of Karen's constant efforts to raise the issue. She raised her concerns during the consultations for the National Rare Disease Plan in Ireland and simultaneously approached the Disability Federation of Ireland on the matter. Epilepsy Ireland came on board to form the Forum in 2014, along with other organisations.

2013	**FACSaware Launch**	**Karen Keely attends the FACSaware Launch with a demonstration at MHRA HQ**
2014	**APPG Thalidomide and harmful drugs.**	**APPG Thalidomide and harmful drugs. APPG Thalidomide and Harmful Drugs.** Alec Shelbrooke hosts FACSaware, OACS, Karen Keely, Karen Buck, FACSA, INFACT, HCP**.**
June 2014	**Secretary General of the Department of Health Meeting**	**Secretary General of the Department of Health** Meeting Joan O Donnell, Karen Keely and other members of the **FACS Forum met with the Secretary General of the Department of Health**. At that meeting several promises were made. Including on **10th June 2014**, we met with the **Sec General at the time, Ambrose Mcloughlin and Pamela Carter**. The Forum did have some follow up email correspondence with **Pamela Carter** to check what the progress **was but we did not receive a report and the last email we received is dated 29 July 2014, promising to "revert to you in a couple of days with an update".** We were also due to have a follow up meeting with the department. **At the meeting, we were assured that the Minister would be made aware of the issue. There was also an agreement that she should meet key decision makers, as she represented parents in Ireland and has three children affected by FACS.** None of this happened: instead a personal email was received from one of the officials who was at the meeting and all attempts form the Forum came to nothing. **False Promises / Missed Opportunity**.
2014	**Personal Letter from DOH**	**Karen Keely received a personal communication from DOH Stating everything is in place for children exposed to Valproate. (Missed opportunity).**
2014	**FACS FORUM meetings with the HPRA**	**FACS FORUM** had meetings with the HPRA in relation to the Forum's concerns on Valproate. **It was stated, at said meeting that Sodium Valproate was first licensed in Ireland in 1983.**
2014	**EMA - PRAC**	**14. Article. EMA PRAC recommendations.** A review of medicines containing sodium valproate undertaken by the European Medicines Agency (EMA) over a two-year period recommended a significant strengthening of restrictions for their use. Product information must now reflect these new recommendations. In a ground-breaking judgment in December 2014, the EMA recommended that sodium valproate should not be prescribed to female children, female adolescents, women of childbearing potential or pregnant women unless other treatments are ineffective or not tolerated.
2014	**Clinical Strategy and Programmes Division Epilepsy**	**Women of childbearing age, pregnant and nursing mothers.** There are important pharmaceutical care considerations in this group due to the potential teratogenic nature of many AEDs and the challenges in managing AED therapy in pregnancy and lactation. There are also clinically significant drug-drug interactions between the AEDs and some contraceptive agents which can be problematic for the management of both indications. Community Pharmacy can form a critical support structure to manage the patient throughout maternity care. **Approved by HSE Leadership 20 June 2016. (Missed Opportunity)**

	Epilepsy Ireland / DFI/ FACS Forum	Karen Keely, Epilepsy Ireland, DFI continues to share concerns and raise awareness thought-out Ireland on the ongoing issues surrounding Valproate in Pregnancy.
2014	**Valproate Five Page Word Document from Sanofi** **For the Irish Pregnancy Prevention Plan Booklet.**	**EMA PRAC recommendations results.** **A booklet has been launched which does not appear to be in widespread use. Ireland did not receive a booklet in 2015 Pregnancy Prevention Booklet / Toolkit. HPRA** Medicines containing valproate: risk of abnormal pregnancy outcomes (Epilim oral range, Epilim Chrono and Epilim IV range)**.** **Dear Healthcare Professional,** This letter is sent in agreement with European Medicines Agency (EMA) and the Health Products Regulatory Authority (HPRA) to inform you of important new information and strengthened warnings related to safety of medicines containing valproate (sodium valproate, valproic. following completion of a Europe-wide review. In agreement with the HPRA, the product information will be updated in due course. **We questioned the HPRA in relation to the UK Toolkit, we asked why Ireland only received a five-page word document. The HPRA stated at the time, that is all they could in Ireland in relation to the Valproate toolkit. (Missed Opportunity)**
2015	**Belfast**	**Karen Keely attends Alcohol and Medications in Pregnancy World Birth Defects Day in Belfast. One day focused on Sodium Valproate. (Missed Opportunity)**

2015	**The OACS Charity UK Tour**	**The OACS Charity and Karen Keely TOUR UK.** Jo Cozens and Karen Keely from OACS, OACS Ireland tour the West Coast from Wales to Scotland and the UK visiting families from OACS and other organisations.
2015	**Epilepsy Ireland conducted two surveys amongst their members**	**Epilepsy Ireland conducted two surveys amongst their members in April 2015.** The first survey received 156 responses, 50% of whom were in the 13-45 age group. The survey revealed a very low level of awareness of the risks they may be exposed to, as well as a low level of medical professional intervention as a result of the EMA ruling. • **Only 3 out of 123 respondents have received a call/ letter from medical team about the issue** • **19 of the 123 respondents say they have an appointment to review medication.** • **43% of people (53 people) have had an appointment since Dec, but of those, Valproate was discussed only at 6 of the 53 appointments** Of those women who knew about the issue, 16% heard it from someone other than their health professional, and 30% heard of it through the awareness raising that Epilepsy Ireland and OACs Ireland have been engaged in. Many only became aware of the issue as a result of doing the survey.
2016	**MHRA**	**MHRA Valproate Stakeholder** engagement meeting at MHRA to discuss Valproate warnings and resources.

2016	**Letters to Minister Health Simon Harris**	**The Forum** have written to the **new Minister for Health twice in 2016** asking to meet and looking for information. **We wrote to Minister Simon Harris initially on 15 June requesting a meeting. His response on 20th June acknowledged our letter** but we received nothing more until we wrote to him again on **29 August, requesting a meeting and also asking him for the following information: Missed Opportunity**
2016	**France**	**France** Supporting our French colleges Jo Cozens, Karen Buck from OACS UK, and Karen Keely from OACS Ireland, attend APESAC press conference in Paris.
2016	**Prescribing trends for sodium valproate in Ireland**	**Prescribing trends for sodium valproate in Ireland**. The rate of prescribing of VPA in Ireland declined slightly from 3.5/1000 per eligible population in 2008 to 3.14/1000 in 2013. While rates of prescribing fell for epilepsy, there appeared to be a rise in prescription for other indications of VPA. In 2013, co-prescription of folic acid or oral contraceptives was relatively low across all community schemes. Finally, an address distant from academic specialist centres predicted a higher exposure to VPA.
2016	**EUROmediCAT signal detection**	**EUROmediCAT signal detection: a systematic method for identifying potential teratogenic medication. Conclusions.** Medication exposure data in the EUROmediCAT central database can be analyzed systematically to determine a manageable set of associations for validation and then testing in independent datasets. Detection of teratogens depends on frequency of exposure, level of risk and teratogenic specificity**.**
JUNE 2016	**HSE RISKS OF VALPROATE**	**Finally, two years after the 2014 review the HSE RELEASES THE RISKS OF VALPROATE IN FEMALE PATIENTS**. Summary Guide for Healthcare Professionals. **Missed Opportunity**
2016	**76th edition of the HPRA**	**The HPRA** published an article in the 76th edition of the HPRA Drug Safety Newsletter (DSN). http://www.hpra.ie/homepage/about-us/publications-forms/newsletters/item?id=23fb0626-9782-6eee-9b55-ff00008c97d0&t=/docs/default-source/publications-forms/newsletters/hpra-drug-safety-newsletter-edition-76 **Missed Opportunity**
2016	**HPRA Valproate Toolkit**	**Valproate Toolkit** This booklet is for you if you are a girl or a woman taking any medicine containing valproate. It contains key information about the risks of valproate in pregnancy. **It has taken the HPRA 2 YEARS TO PRUODUCE THIS TOOLKIT WHEN UK GOT THERE'S IN 2014. Ireland received a 5-page word document. Missed Opportunity**
2016	**Sanofi**	**Representatives from the Forum met with Sanofi in September 2016. The Forum raised the issue of supports for families already affected as well as better warnings on the patient information and Healthcare Professionals.** Sanofi representatives stated that they did not accept any liability for what had happened to children. They saw it as a HCP issue. They sympathised with those affected but did not see a role for themselves in supporting them. They were instead interested in public health information. The Forum members still have an expectation that Sanofi will provide meaningful proposals in order to support families affected by taking Epilim and we wrote to them to reiterate this on 22 December 2016. **Missed Opportunity**

2017	**Epilepsy Ireland's**	**Epilepsy Ireland's survey of women taking valproate found that just 56% of them had had discussions about valproate risks with their medical team in the past three years.**
2017	**MHRA**	**MHRA Valproate Stakeholders Meeting.** OACS Ireland attend the MHRA Valproate Stakeholders Meeting.
2017	**ASSAC**	**Conference in Switzerland, attended by FACSaware, OACS, OACS Ireland, APESAC, ABVSV.**
2017	**Presentation to the European Medicines Agency**	**Presentation to the European Medicines Agency on behalf of the FACS Forum Ireland Karen of the FACS Forum Ireland addressed the EMA's public hearing on valproate in London.** The hearing was investigating whether 2014 European-wide measures to restrict the use of valproate in girls and women of childbearing potential have been effective and whether additional measures to reduce risks associated with the drug are needed. "In Ireland, the HPRA and HSE have taken some measures to improve awareness of the risks and to improve communication between patients and health professionals, these have largely been tick-box exercises with little regard for delivering real change.
2017	**HPRA**	**HPRA DSN Valproate** The latest edition of the HPRA Drug Safety Newsletter (DSN) includes important updates to support the safe and appropriate use of the following medicines: Valproate (Epilim) and Developmental Disorders: Update on ongoing EU review. Domperidone-containing medicines: reminder of the risk of cardiac adverse reactions-restricted indication, contraindications and reduced dose and duration of use New CPD e-learning module on reporting suspected adverse drug reactions. Direct Healthcare Professional Communications published on the HPRA website since the last Drug Safety Newsletter. Download: hpra-drug-safety-newsletter-edition-81.pdf
2017	**France TV Envoye Special**	**France TV Envoye Special takes places Watford** with APESAC, FACSaware and OACS Charity, Karen Keely attends on behalf of the FACS Forum for the France TV Envoye Special and other families impacted.
2017	**Disability Campaign groups in particular OACS Ireland, Epilepsy Ireland, and Disability Federation of Ireland**	**Disability campaign groups call for greater warnings on epilepsy drug boxes.** "The most effective way of ensuring that all women and parents of girls taking the drug know the risks is to make it clear on the outside of the box. In recent years, there has been a comprehensive warning on the leaflet inside, but many people never read those, especially people on the drug long-term", said Ms Keely, who has three sons diagnosed with Fetal Anticonvulsant Syndrome**. Peter Murphy, CEO of Epilepsy Ireland** who are also members of the FACS Forum said: "It is only three years since the European Medicines Agency (EMA) laid down new regulations to be implemented across Europe to minimise the risks associated with valproate, but only last month, they announced a fresh review amid concerns that the existing measures were not proving effective. It is time to give this issue the priority it deserves and ensure that every possible step is taken to prevent future cases of FACS".
2017	**Epilepsy Ireland**	**Epilepsy Ireland acknowledges the hard work of OACS**

		International Women's Day OACS - Speaking up for mothers On International Women's Day, Epilepsy Ireland were delighted to highlight the invaluable work done by the OACS (Organisation for Anticonvulsant Syndromes Ireland) organisation in supporting and representing women with epilepsy.
2017	**OACS Ireland Epilepsy Ireland.**	**OACS Ireland Epilepsy Ireland.** Continuously approach the Irish Government in relation to an Independent Inquiry and/or Investigation into the Historical use of Epilim (valproate) in Ireland.
2017	**Sensitivity of the UK Clinical Practice Research Datalink**	**Sensitivity of the UK Clinical Practice Research Datalink to Detect Neurodevelopmental Effects of Medicine Exposure in Utero: Comparative Analysis of an Antiepileptic Drug-Exposed Cohort METHODS:** A cohort of mother-child pairs of women with epilepsy (WWE) was identified in the CPRD and matched to a cohort without epilepsy. The study period ran from 1 January 2000 to 31 March 2007 and children were required to be in the CPRD at age 6 years. AED exposure during pregnancy was determined from prescription data and children with an NDD diagnosis by 6 years were identified from Read clinical codes. The prevalence and risk of NDDs was calculated for mother-child pairs in WWE stratified by AED regimen and for those without epilepsy. Comparisons were made with the results of the prospective Liverpool and Manchester Neurodevelopment Group study which completed assessment on 201 WWE and 214 without epilepsy at age 6 years.
2018	**HPRA Meeting**	**Valproate Stakeholders Meeting HPRA**, Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace. Discussions on the new EMA measures and warnings. One and only meeting relating to said measures. The said measures were handed over to the HSE.
2018	**Award Epilepsy Ireland Volunteer Awarded by CEO Peter Murphy.**	**Epilepsy Ireland Recognised Karen Keely's work.: Volunteer Karen Keely at the National Conference** The consequences of sodium valproate have dominated her life. Her sons have all had repeated medical, surgical and clinical interventions and two require lifelong care. Despite all the difficulties and challenges that this has brought, and the battles she has had to endure for her family, Karen has for the past **decade** devoted herself to raising awareness among other **Irish women with epilepsy of the risks of valproate and fighting for recognition and justice for the families affected.** Who would go to the ends of the earth not just for her own boys but for all the mums and children out there who are similarly affected or who are at risk. Awarded by CEO Peter Murphy Award
2018	**Oireachtas**	**Oireachtas: A/V Room Mothers spoke before Members of Irish Government WHICH INCLUDED Senators and TD'S**
2018	**Oireachtas Health Committee on Foetal Anticonvulsant Syndrome.**	**FACS Forum appeal for action at health Committee**. Which included **Peter Murphy CEO of Epilepsy Ireland**, **Joan ODonnell (DFI)** and **Karen Keely Chairperson OACS Ireland** spoke today at a health committee on Foetal Anticonvulsant Syndrome. Karen Keely of OACS Ireland, who three sons all had birth defects after she took sodium valproate read out emotional statements on behalf of other Mothers who have been affected by the drug.

		Many of the families attended the hearing. Minister for Health Simon Harris last week stated that parents affected by the drug sodium valproate have been 'let down' after the issue was raised in the Dáil by Fianna Fail TD, Bobby Aylward. The full hearing can be watched on oireachtas.ie
2018	**Awareness and documentation of the teratogenic effects of valproate among women of child-bearing potential. Ireland**	**Awareness and documentation of the teratogenic effects of valproate among women of child-bearing potential.** Deirdre Mulryan, Anna McIntyre, Colm McDonald, Sabina Feeney, Brian Hallahan BJPsych Bulletin (2018). **Our findings of poor clinical documentation of specific risks of valproate are consistent with previous research, with rates of 16–29% nSoted for documentation of risks of teratogenesis or the provision of advice in relation to contraception for women of child-bearing potential who are prescribed valproate. Similarly, documented advice in clinical notes relating to the use of folic acid has previously also been noted to be particularly low (4%). Our findings in relation to patient awareness of teratogenic risks of valproate are also consistent with previous studies (17–28%); however, awareness of the need for contraceptive use was lower in our patient cohort compared with a number of previous studies (55–67%). Missed Opportunity**
2018	**JOINT COMMITTEE ON HEALTH Report on Foetal Anti-convulsant Syndrome Outcome**	**JOINT COMMITTEE ON HEALTH Report on Foetal Anticonvulsant Syndrome**. It is noted that individuals with FACS **are not affected by chance but by the failure to adequately inform and counsel women who were prescribed valproate medicines. A lack of appropriate preventative measures resulted in numerous cases of FACS in Ireland**. It will take time and resources to examine these areas. However, the Committee are anxious that some areas are addressed as a matter of urgency. **Further examination is required to establish liability but regardless of the causes, the Committee is of the opinion that the State has responsibility to assist all those affected by FACS.** **11. The Committee recommends the establishment of an independent investigation to examine the historical use of valproate medicines in Ireland and into the ongoing effects of valproate medicines.** **12. The Committee recommends that further consideration and examination is undertaken with regard to compensating FACS patients.**
2018	**OACS Ireland the story of Far.**	**OACS Ireland the story so far.** OACS Ireland and Epilepsy Ireland attend many ongoing meetings in the Irish Government along with many other Irish mothers who are impacted by Epilim (Sodium Valproate) With great thanks to all mothers involved. https://www.youtube.com/watch?v=ADxmxtrHJOo
2018	**Epilepsy Ireland and OACS Ireland Campaign**	**Epilepsy Ireland and OACS Ireland continues to campaign for all valproate prescriptions to be dispensed in original external packaging which has the EU-approved warnings. Unfortunately,**

	#EpilimInABag	**this is still not always happening in Ireland, as can be seen in photos published on Twitter recently under the #EpilimInABag hashtag.**
2018	**Senator Rose Conway-Walsh is calling for an independent inquiry into sodium valproate (Epilim)**	**Senator Rose Conway-Walsh is calling for an independent inquiry into sodium valproate (Epilim)** – an epilepsy drug linked to birth defects. Rose Conway-Walsh told The Times Ireland Edition that a "do-nothing" approach was not acceptable. **Last June, an Oireachtas report backed an independent inquiry into the controversy. The Committee, chaired by Dr Michael Harty TD, emphasised their support for those affected and made a number of recommendations which included "the establishment of an independent investigation to examine the historical use of valproate in Ireland and into its ongoing effects. Ms Conway-Walsh said that the state must establish a redress scheme to meet "the lifelong care needs of children and the impact of diagnosis on families." "I know families who desperately need therapies and treatment, but they cannot afford them. They sit and watch while their children regress. This is an intolerable situation and must stop."**
	The Pharmaceutical Society of Ireland	**Niall Byrne, Registrar of the PSI states: "We cannot overstate the importance of informing patients of the risks associated with medicines containing valproate, which are used in the treatment of epilepsy and bipolar disorder.** **Mr Byrne added: "Patients must be counselled and provided with a Package Leaflet and Alert Card on each occasion these medicines are supplied. Anything less than this is not acceptable. If a member of the public has any concerns, they should contact us on valproate.concerns@psi.ie or call 01-2184000."** **Epilepsy Ireland and OACS Ireland welcomes this move by the PSI. We would strongly encourage anyone who receives valproate from now on without the leaflet or the alert card to report the incident to the PSI. Even today, it cannot be assumed that all women taking this drug are aware of the risk.**
2018	**VPG Initiates**	**Valproate Project Group Commences.** Due to the outcome of the Health Committee on FACS and the ongoing work of OACS Ireland Epilepsy Ireland.
2018	**OACS Ireland and Epilepsy Ireland**	**OACS Ireland and Epilepsy Ireland continuously have meetings with the Valproate Project Group.**
2018	**Fetal valproate syndrome: the Irish experience**	**"Another interesting fact that arose from our record is that the majority of the women have been on VPA [valproate] since diagnosed with epilepsy (mostly since childhood). The medication was not changed due to the stability of their condition…There was a big possibility that the patients were not aware regarding the higher dose of folic acid supplementation, the teratogenicity effect of the VPA and the need of contraception". Fetal valproate syndrome: the Irish experience.**
1975 - 2019	**HPRA Summary details of**	**Summary details of suspected adverse reactions/events reported to the HPRA in association with Epilim/Sodium**

	suspected adverse reactions/events.	**Valproate/Valproic Acid 01/01/1975-30/06/2019.** **We found 68 cases of FVS in the report.** **17 before 2010.** **41 since 2010.** **(It then begs the question why no-one raised the alarm sooner missed opportunity)**
2019	**OACS Ireland Epilepsy Ireland**	**OACS Ireland / Epilepsy Ireland. Continuously approach the Irish Government in relation to an Independent Inquiry and/or Investigation into the Historical use of Epilim (valproate) in Ireland.**
2019	**Rapid Assessment Report 1975-2015**	**Rapid assessment of the number of women and children exposed to sodium valproate in Ireland 1975-2015.** It is estimated that, between 1975 and 2015, inclusive, approximately 3,083 (3,058 epilepsy; 25 other indications) maternities were in women who were taking valproate when becoming pregnant. On the basis of the above estimations and on emerging international data regarding rates of major congenital malformation and neurodevelopmental delay following exposure to valproate in utero, it is estimated **that between 1975 and 2015, between 153 and 341 children will have experienced a major congenital malformation and up to 1,250 children will have experienced some form of neurodevelopmental delay. Of children born since 2000, it is estimated that between 43 and 95 will have experienced a major congenital malformation and 349 will have experienced some form of neurodevelopmental delay; a similar number of children, born between 2002 and 2017 and currently aged 0-16, are likely to have experienced such a malformation and/or delay**. It should be emphasised that there is no single source of data relating to the use of valproate.
2019	**The HSE FINAL Report**	**The HSE FINAL Report form the Chair of the Valproate Project Group Report. Written by Ms Deirdre McNamara HSE. NOT Published Yet. Families left in limbo. (Missed Opportunity).**
2019 / 2020	**An Easy guide to Rare Diseases in Ireland. (not sure whether to add this or not)**	**An Easy guide to Rare Diseases in Ireland.** **For Government, the General Public, Media and Political Parties** Published by Patient Groups concerned with Rare Diseases and Consensus for Action. **FVS - Foetal Valproate Syndrome (see Annex 4)** is a range of devastating birth defects that can occur from the side effects of taking an anti-epilepsy or other drugs which contain valproic acid (VPA) during pregnancy. **Despite studies dating back to the 1980's, both industry and national governments across the world (including Ireland), were slow to act on overwhelming evidence of the side effects of such drugs, including Epilim.** Progress on addressing this issue is thanks to the advocacy of one Irish parent, Karen Keeley. Thanks to Karen and the patient advocacy group she founded, the Organisation for Anticonvulsant Syndrome (OACS) Ireland, combined with a European Medicines

		Agency judgement in February 2018. Karen's advocacy work was also given important support from groups involved in the Rare Disease Taskforce, which include Epilepsy Ireland, through the FACS Forum Ireland.
2020	**Valproate / Epilim MEDIA**	**Catherine Riley** is the News Editor with the Medical Independent, Ireland's leading investigative medical newspaper (www.mindo.ie). Catherine has also written for The Irish Times, Sunday Business Post, Irish Medical Times and Fingal Independent. Catherine has been reporting on issues on an ongoing basis. http://www.catherinereilly.com/valproateepilim-scandal.html
2020	**MHRA**	**MHRA meeting Valproate pregnancy register UK.**
2020	**OACS Ireland Manifesto #GE2020**	**2020 Manifesto #GE2020** **OACS Ireland would like assurances from the next Government that the following points are met in full. Acknowledgement for Families impacted!** **EPILIM (Sodium Valproate) Epilim (Sodium Valproate) has been licensed in Ireland since 1975, families impacted want to know why Ireland has failed to acknowledge the hurt, pain, suffering, distress, anguish, trauma, torment and grief. This is only some of the damage that Epilim (Sodium Valproate) has caused.**
2020	**POINT 6. Epilepsy Ireland Manifesto. 6. #GE2020**	**POINT 6. Epilepsy Ireland Manifesto. 6. #GE2020** **The full implementation of the Oireachtas Committee on Health recommendations on Sodium Valproate and foetal anti-convulsant syndrome (FACS) including the provision of supports for families affected by FACS. This issue, which affects up to 1,200 Irish families also requires further investigation by the State to provide answers to the families and to ensure that this situation is not repeated in the future.**
2020	**Epilepsy Ireland - Survey**	**Epilepsy Ireland and OACS Ireland have met with HPRA**. Epilepsy Ireland and OACS Ireland have met with HPRA to discuss need for further risk minimisation measures in light of the outcome of the Epilepsy Ireland survey. **OACS/EI recommended the establishment of Valproate Stakeholder Group to work collaboratively to improve the effectiveness of risk minimisation measures.** The survey found that three in 10 women have never had a discussion with a health care professional about the risks of valproate in pregnancy; only one in four women had ever heard of the Pregnancy Prevention Programme, a mandatory requirement for all female patients; while one in six women were not aware of the risks at all. Other findings on www.epilepsy.ie from 1 July 2020.
2020	**HPRA -May**	The HPRA issued new DSN on valproate, May 2020 based on the teratogenic effects of Epilim (Sodium Valproate). **Summary of Teratogenic Risks-** drug-safety-newsletter-97th-edition.pdf
2020		

OACS Ireland June 2020

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Q: As you are aware both the January 1983 Current Problems and the February 1984 WHO Bulletin[1] considered the Rhône-Alps data, and neither concluded that this study identified valproate as a more potent teratogen than other AEDs. However, in November 1984 DiLiberti et al.[2] published case reports describing 'Foetal Valproate Syndrome'.

We are particularly interested in Sanofi's perception of the risks associated with valproate exposure in the time period between the WHO bulletin in February 1984 and the end of that year. Please can you share any relevant documents (received from or sent to external sources, or generated or circulated internally within the company) that would assist us in determining how the risk was perceived and how the understanding of the risks evolved.

As previously indicated, in view of the fact that over 35 years has elapsed, Sanofi has very few documents relating to the period referenced in your email. Furthermore, any investigation is made more difficult by the restrictions imposed as a result of the current COVID-19 crisis. Our response to your inquiry is therefore provided below, subject to these provisos.

The WHO bulletin published in February 1984, included a section entitled "Valproate and Pregnancy" which considered the implications of the Rhône-Alps data and also noted the potential biases arising from that study. In circumstances where the association reported in the Rhône-Alps analysis had either not been confirmed or had been rejected by other surveys undertaken in France, Italy and in South America, the bulletin concluded that the Rhône-Alps data did not identify sodium valproate as a more potent teratogen than other anti-epileptic drugs and noted that *"no Regulatory Authority has consequently reacted to restrict the use of valproate during pregnancy when it is likely to be effective and when a measure of seizure control is considered necessary"*.

Sanofi is not, at this stage, aware of any additional material publications or analyses that contributed to knowledge regarding the effects of valproate in utero, that emerged during the period covered by your request.

You refer to the paper by DiLiberti et al, published in November 1984 (Diliberti, JH et al. The Foetal Valproate Syndrome. Am J Med Genet 1984; 19(3) 473), which is often cited as the first occasion when the possibility of "fetal valproate syndrome" was suggested. Sanofi provided comments on this paper in the response to Question 7 of the valproate section of the Review's Call for Evidence sent to us on 19 September 2018. Diliberti describes seven cases, selected because they had been exposed to sodium valproate in utero (i.e. knowledge of exposure preceded the assessment) and suggests that they had an abnormal and consistent facial phenotype. This observation was not however generally accepted (see e.g. Chessa L and Iannetti P. Fetal Valproate Syndrome. Am J Med Genet. 1986 Jun;24(2):381-2) and the existence of a fetal valproate syndrome remains controversial today.* The seven cases described are heterogeneous and only limited information is available: three of the children were exposed to other anti-epileptic drugs as well as valproate; four of the seven children had no problems other than the alleged facial abnormalities, whereas three had some of various other anomalies (hypospadias, patent ductus arteriosus, intermittent esotropia and bilateral inguinal hernia). Three of the described children (only two are mentioned in the summary

[1] A bulletin issued by the World Health Organisation ("WHO"), "Drug Information January - December 1983", included a section entitled "Valproate and Pregnancy" – *from written evidence provided by Sanofi*

[2] DiLiberti, JH et al. The Foetal Valproate Syndrome. Am J Med Genet 1984; 19(3) 473

and abstract) were also said to have developmental delay, although few details were provided and the findings were consistent with the presence of other factors in all three cases (such as maternal epilepsy and epilepsy of the child, polytherapy, epileptic seizures during pregnancy, preeclampsia and reduced foetal growth rate). The Review is aware that case reports are subject to substantial confounding and are viewed as the lowest hierarchy of evidence and the overall interpretation of this paper is made even more difficult in circumstances where epilepsy may be associated with genetic disorders (two of the seven cases were siblings, increasing the probability of a genetic cause) and genetic tests were not generally available at that time.

* A syndrome is generally defined as a group of symptoms which consistently occur together, or a condition characterized by a set of associated symptoms. Children exposed to valproate in utero however may experience a wide range of different effects and there is no specific symptom or effect present in all affected children. In these circumstances the condition may not satisfy the requirements for a syndrome and a number of experts prefer the term "valproate spectrum disorder".[3]

[3] See e.g. Clayton-Smith J et al. Diagnosis and management of individuals with Fetal Valproate Spectrum Disorder; a consensus statement from the European Reference Network for Congenital Malformations and Intellectual Disability. Orphanet Journal of Rare Diseases 2019; volume 14, Article number: 180