Annex H: History of Regulation

Contents

1. Regulatory background 1950 to date

1.1. Introduction

1.1.1. Start dates for Key events relevant to IMMDS Review are outlined in Table H.1. This shows that the three interventions within this review span a substantial time period.

Start Date	Event
5 July 1948	The NHS began
1953	HPTs on the UK market (withdrawn in 1978)
1 Jan 1964	Voluntary self-regulation of drugs (in place until formalised regulation)
1 Sept 1971	Formalised medicine regulation begins under Medicines Act 1968
1972-3	Valproate launched in the UK
1 Jan 1973	UK joined EEC (EU medicine regulation applied in UK)
12 July 1993	First EU Medical Devices Directive
Mid 1990s	First Stress Urinary Incontinence mesh kits launched
Early 2000s	First Pelvic Organ Prolapse mesh kits launched

Table H.1 Start dates of key events relevant to the IMMDS Review

1.1.2. The regulation of both medicines and medical devices has changed substantially since the 1950s. The following description gives a brief outline of the relevant regulation and organisations throughout this time period.

1.1.3. The Government Department with responsibility for the nation's health has had different names and has included additional functions over time, see Figure H.1

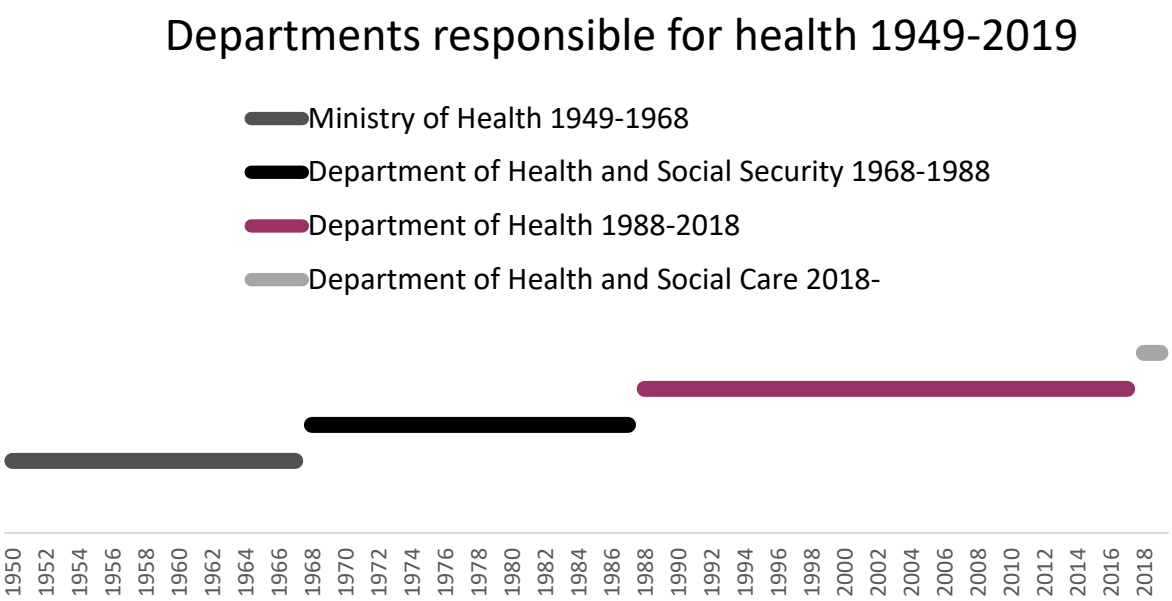

Figure H.1 Departments responsible for Health 1950 to date

2. Medicines

2.1. National regulation of medicines

2.1.1 Medicinal practice, pharmaceuticals and medicinal devices across the UK and in the devolved nations can be regulated via several mechanisms, see Figure H.2.

Primary legislation. The main laws passed by the legislative bodies of the UK, including the UK Parliament. Secondary legislation. Secondary legislation is law created by ministers (or other bodies) under powers given to them by an Act of Parliament. Secondary legislation is sometimes known as 'delegated' or 'subordinate' legislation and often takes the form of a statutory instrument. Court precedents. Decisions taken by the higher UK courts can create precedents on the interpretation and application of the law, which may then be binding on certain legal cases Other 'soft' regulation. This can take a variety of forms and have a range of different sanctions, and includes, for example, some of the guidance produced by the professional regulators such as the GMC, the NMC and the Royal Colleges.

Figure H.2 Types of regulation in the UK

2.1.2 The UK organisations that have been key to the regulation of the interventions under review are detailed in Figure H.3, and will be briefly described below.

Dates	Organisation	Legal Status	Primary Purpose	Powers
Pre-1968	None	-	-	-
06/1968 – 08/1971	Committee on Safety of Drugs **(CSD)**	Non Statutory (Voluntary by agreement with the pharmaceutical industry)	To **advise** on drug safety and to create **and administer** a **voluntary** licencing structure	**None** – could ask manufacturers to remove a medicine, could not make them
09/1971 – 10/2005	Medicines Commission	Statutory under Medicines Act 1968 as per Directive 75/318/EEC	To **advise** the licencing authority on issued related to the 1968 Act	Advised the Licencing authority – in particular on the setting up of committees, such as CSM and CRM and on appeals by manufacturers
09/1971 – 10/2005	Committee on Safety of Medicines **(CSM)**	Statutory under Medicines Act 1968	To **advise** the licencing authority on drugs	Advised the Licencing authority on drug efficacy, safety and quality
10/2005 -	Commission on Human Medicines **(CHM)**	Statutory under Medicines Act 1968 (SI 2005 No. 1094) as per Directive 75/318/EEC	**Advisory** - Amalgamated roles of Medicines Commission and CSM (MHRA provides admin support for CHM)	As for Medicines Commission and CSM
2001 – Aug 2014	Committee on Safety of Devices	Non-Statutory (Voluntary arrangement with various devices experts)	To **advise** the Competent Authority on devices	Advisory, no powers, could make recommendations
Sept 2014 -	Devices Expert Advisory Committee **(DEAC)**	Non-Statutory (Voluntary arrangement with various devices experts)	To **advise** the Competent Authority (MHRA) on devices	Advisory, no powers, could make recommendations

09/1971-03/1989	Medicines Division of the Department of Health and Social Security (DHSS)	Statutory under Medicines Act 1968 as per Directive 75/318/EEC	**Administrative agency** for licencing medicines	Responsible for licencing including ability to remove medicines. Mission statement – To promote and safeguard public health through ensuring appropriate standards of safety, quality and efficacy for all medicines on the UK market. from the market
04/1989-03/2003	Medicines Control Agency **MCA**	Statutory under Medicines Act 1968 as per Directive 75/318/EEC	**Administrative agency** for licencing medicines	Responsible for licencing including ability to remove medicines. Mission statement – To promote and safeguard public health through ensuring appropriate standards of safety, quality and efficacy for all medicines on the UK market. from the market
1969 – 08/1994	The Scientific and Technical Board (STB) of the Department of Health, the Medical Devices Directive (MDD) of the Department of Health and the Medical Devices Agency (MDA).	Non-statutory	**Quasi-regulatory** Checking devices were safe and met appropriate standards	To protect public health and safeguard the interest of patients and users by ensuring that medical devices and equipment met appropriate standards of safety, quality and performance and that they complied with relevant rules.
09/1994 - 03/2003	Devices Control Agency (D**CA)**	Executive Agency enforcing statutory provisions.	**Regulatory** Checking compliance with regulatory	To ensuring that medical devices and equipment complied with relevant laws designed to ensure they met appropriate

			standards for devices	standards of safety, quality and performance.
04/2003-	Medicines and Healthcare Regulatory Agency (**MHRA)**	Statutory under Medicines Act 1968 as per Directive 75/318/EEC	**Administrative agency** for medicines licencing & Devices. Merger of MCA and DCA	Responsible for licencing, including ability to remove medicines and devices from the market
10/1975 – 03/1992	Committee for the Review of Medicines (**CRM)**	Statutory under SI 1975/1066 as per Directive 75/318/EEC	To review medicines which were marketed in the UK prior to 22/11/1976 for quality, safety and efficacy	Could convert a Product Licence of Right (PLR) to a full licence or could remove the PLR.

Figure H.3 Key National Organisations in the control of the pharmaceuticals and Medical Devices being reviewed by the IMMMDS Review.

2.2. European regulation of medicines

2.2.1 On 1 January 1973 Great Britain joined the EEC. Under the architecture of the EU, there are different types of legislation passed at EU level which place different requirements on member states, see Figure H.4

Regulations. A Regulation is a binding legislative act. It must be applied in its entirety across the EU.
Directives. A Directive is a legislative act that sets out a goal that all EU member states must achieve. However, each individual member state is responsible for designing and implementing their own laws to achieve these goals.
Decisions. A decision is binding on those to whom it is addressed (e.g. an EU member state or an individual agency/company) and is directly applicable (meaning it does not need any other act of parliament in the relevant member state to make it into a law).
Recommendations. A recommendation is not binding on those to whom it is addressed. A recommendation suggests a course of action without imposing any legal obligation to follow that course of action.
Opinion. An opinion is not binding on those to whom it is addressed. An opinion allows various institutions to state an opinion about a topic, without imposing any legal obligation.

Figure H.4 Types of regulation in the EU

2.2.2 The UK domestic legislation has therefore been aligned with the EU requirements since 1973. Since then the EU has grown to include (at present) 27 member states.[1]

2.2.3 At the time of writing Great Britain is no longer a member of the EU, but continues to be subject to EU rules and remains a member of the single market and customs union. The UK remains subject to EU law and the rulings of the European Court of Justice throughout the transition period. The impact of Brexit on pharmaceutical and medical device regulation is yet to be fully ascertained.

2.2.4 The framework of the EU medicines (and medical devices) legislation focusses on creating a fair transparent market place for these products. However, the regulatory requirements also address the safety of these products. The scope of the relevant EU legislation has been extended regularly, to incorporate more and more extensive pre-marketing controls and extensive post-marketing safety surveillance system.

2.3. UK Pharmaceutical regulation up to and including the 1950s

2.3.1 In the 1950s there was very limited pharmaceutical regulation. Certain pharmaceuticals were regulated, for example

- Drugs and poisons on the 'Poisons List' under the Pharmacy and Poisons Act 1933
- Biologicals (vaccines, sera, extracts, etc) under the Therapeutic Substances Act 1925
- Opiates and Cocaine under the Dangerous Drugs Act 1920
- Penicillin under the Penicillin Act 1947.

2.3.2 However, there was no centralised structured pharmaceutical regulation. Regulation tended to be either for specific products, as set out above, or related to specific diseases[2], There was no general consumer protection legislation either, this appeared much later and after the accession of the UK to the EU (EEC as was).

2.3.3 When Hormonal Pregnancy Tests were placed on the UK market in the 1950s and 1960s:

- no licence was required,
- no specific safety tests were needed,

[1] 01/01/1958 – Belgium, France, Germany, Italy, Luxembourg, Netherlands; 01/01/1973 – Denmark, Ireland, United Kingdom (left 31/01/2020); 01/01/9181 – Greece; 01/01/1986 – Portugal, Spain; 01/01/1995 – Austria, Finland, Sweden; 01/05/2004 – Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovakia, Slovenia; 01/01/2007 – Bulgaria, Romania; 01/07/2013 Croatia

[2] For example, the Venereal Diseases Act 1917 and the Cancer Act 1939 respectively prevented the advertising and sale of medicines for that specific condition and outlawed the giving advice of or treatment of those conditions by those who were not medical practitioners.

- no specific proof of efficacy was required.

2.3.4 It had long been recognised that the system of pharmaceutical regulation was inadequate and in need of overhaul. This was all to painfully highlighted by the Thalidomide disaster.

2.4. Thalidomide (1958-62), the informal response and the Medicines Act 1968

2.4.1 Thalidomide was marketed in the UK between April 1958 and September 1962. The regulatory response to the thalidomide tragedy was two-fold initially a voluntary response, and a later statutory response.

2.4.2 The voluntary response, the Committee on Safety of Drugs, started in 1963.

2.4.3 The formal statutory response to thalidomide took longer. In September 1967 a white paper was put forward outlining a new regulatory structure and organisations. This became the Medicines Act 1968, which received royal assent in October 1968.

2.4.4 A transitional period was put in place until the Act became effective to allow for adjustment to the new system. The date from which the law was in force (also known as the effective date) of the Medicines Act 1968 was 1 September 1971.

2.5. The transitional period. 1968-1971

2.5.1 Under the transitional period from the Medicines Act 1968 receiving royal assent in October 1968 to the effective date of the 1968 Act on 1 September 1971 there was no formal regulator, and no body that could legally mandate the removal of a drug from the market. There were limited mechanisms to regulate drugs and restrict their use. One option was classifying them as a poison and adding them to the 'poisons list' which restricted availability. Alternatively, a medicine could be removed from the market voluntarily by the manufacturer/distributor, as had happened with Thalidomide.

2.5.2 Throughout the transitional period all new medicines were assessed by the Committee on Safety of Drugs (CSD). Medicines that were already on the market were also assessed if there was a concern about their safety, as happened with HPTs.

2.6. Committee on Safety of Drugs (CSD)

2.6.1 Also known as the Dunlop Committee after Sir Derek Dunlop who chaired it, the Committee on Safety of Drugs (CSD) was established in June 1963 and held monthly meetings from January 1964 until 1 September 1971. CSD assessed all new drugs and some pharmaceuticals where there were reports of side effects and safety concerns.

2.6.2 Any recommendations made by the committee were non-binding and the Committee had no power to remove a drug from the market. CSD was not a regulator, it was part of a voluntary arrangement.

2.6.3 Although they had no formal legal power the recommendations made by CSD were adhered to by the major pharmaceutical manufacturers. Both the Association of British Pharmaceutical (ABPI) and the Proprietary Association of Great Britain (PAGB) required their members to adhere to the CSD recommendations.

2.6.4 The terms of reference for CSD are below.[3]

1) To invite from the manufacturer or other person developing or proposing to market a drug in the United Kingdom any reports they may think fit on the toxicity tests carried out on it; to consider whether any further tests should be made and whether the drug should be submitted to clinical trials; and to convey their advice to those who submitted the reports
2) To obtain reports of clinical trials of drugs submitted thereto.
3) Taking into account the safety and efficacy of each drug, and the purposes for which it is to be used, to consider whether it may be released for marketing, with or without precautions or restrictions on its use; and to convey their advice to those who submitted reports.
4) To give manufacturers and others concerned any general advice they may think fit on the matters referred to in paragraphs 1-3.
5) To assemble and assess reports about adverse effects of drugs in use and prepare information thereon that may be brought to the notice of doctors and others concerned
6) To advise the appointing ministers on any of the above matters

2.6.5 The majority of these apply to new to market drugs. There are specific mentions of informing those who have submitted reports, manufacturers, doctors, ministers and 'others

[3] *Medical News.* British Medical Journal, 1963. **1**(5344): p. 1554-1556.

concerned'. There is no definition of 'others concerned'. There is no specific mention of informing members of the public, though they could be 'others concerned'.

2.6.6 The CSD was served by various subcommittees, which also met monthly. The three most prominent subcommittees were:-

- The Toxicity Subcommittee, chaired by Professor Frazer, which considered aspects related to animal testing.
- The Clinical Trials subcommittee, chaired by Prof Robert Hunter, which advised on the conduct of clinical trials.
- The Adverse Reactions Subcommittee, chaired by Prof. Leslie Witts which considered reports of adverse drug reactions.

2.7. The Medicines Act 1968

2.7.1 As of 1 September 1971 the Medicines Act 1968 was effective. The CDS was replace by the statutory Committee on Safety of Medicines. The Licencing Authority (which had statutory powers) came into being. Drug regulation was formalised, centralised and more effective

2.7.2 All new medicines required a licence, and at section 19(1) (as originally enacted) the factors relevant to the determination of an application for a licence were laid out[4] and include a focus on the safety, efficacy and quality of the medicinal product for the purpose for which it was licenced.

Subject to the following provisions of this Part of this Act, in dealing with an application for a product licence the licensing authority shall in particular take into consideration—

a. the safety of medicinal products of each description to which the application relates ;
b. the efficacy of medicinal products of each such description for the purposes for which the products are proposed to be administered ; and
c. the quality of medicinal products of each such description, according to the specification and the method or proposed method of manufacture of the products, and the provisions proposed for securing that the products as sold or supplied will be of that quality.

2.8. The Licencing Authority

[4] Medicines Act 1968, s19(1)

2.8.1 The Licensing Authority were responsible for the regulation of drug safety, efficacy and quality. The Licensing Authority had the legal powers necessary to approve drugs and, crucially, to suspend, vary or revoke marketing authorizations, enabling them to remove drugs from the market.[5] Initially the Licencing Authority comprised the Secretaries of State for Health and Agriculture and the Secretary of State for Scotland.

2.8.2 The Licencing Authority has always acted for the entire United Kingdom. Licensing was a reserved function under the Scotland Act 1998, and although devolution altered the composition of the Licencing Authority, it continues to act for the whole of the UK.

2.8.3 The Licensing Authority has always delegated its authority, initially to the Medicines Division of the Department of Health and Social Security (DHSS), then from 1 April 1989 to the Medicines Control Agency, which merged with the Medical Devices Agency on 1 April 2003 to form the MHRA.

2.9. Medicines Division of the DHSS

2.9.1 Although the Licencing Authority had final responsibility they did not conduct the day to day functions, initially these were delegated to the Medicines Division of the Department of Health and Social Security.

2.9.2 When Reckitt & Colman (trading as Reckitt-Labaz Ltd) applied for a licence on behalf of Pharmacy Products UK Ltd 1972 the licencing process was administered by the Medicines Division, with advice from the Committee on Safety of Medicines, according to the provisions of the 1968 Medicines Act.

2.10. Committee on Safety of Medicines

2.10.1 To assist the Licensing Authority the Committee on Safety of Medicines (CSM) took over the functions previously undertaking by the CSD. New product licence applications were considered by CSM, using the above criteria of safety, efficacy and quality.

2.10.2 Products that had been on the market before the 1 September 1971 were automatically granted a License of right.[6] Product Licences of Right were valid for a transitional period, after which PLR holders were obliged to apply for a new licence, see below.[7]

[5] Medicines Act 1968, s 28.
[6] Medicines Act 1968, s 25-27.
[7] Medicines Act 1968, s 16-17 and 25-27.

2.10.3 The Committee on Safety of Medicines provided support for licencing decisions from the 1 September 1971 until 30 October 2005 when it was replaced by the Commission on Human Medicines. The vast majority of applications were processed without being referred to CSM: CSM were asked to consider all new drug applications as well as other more complex cases.

2.11. Accession to the EEC (1 January 1973)

2.11.1 When the UK joined the EU Directive 65/65/EEC[8] governed the marketing of pharmaceuticals. The Medicines Act 1968 broadly mirrored the requirements of Directive 65/65/EEC, so the transition into the EU regulatory system was relatively seamless.

2.11.2 In order to place a medicine on the market of an EU member state a marketing authorisation had to have been issued by the Competent Authority (CA) of that Member State. In the UK the Competent Authority[9] comprised the Licencing Authority. The UK Licensing Authority has always delegated its authority, so the UK Competent Authority was initially the Medicines Division of the Department of Health and Social Security (DHSS), then the Medicines Control Agency, and then the Medicines and Healthcare Regulatory Authority, MHRA, became the Competent Authority for both medicines and devices.

2.12. Product Licences of Right (PLR)

2.12.1 Since they were first issued it had been recognised that Product Licences of Right needed to be reviewed as these medicines had never been required to submit evidence of quality, safety or efficacy.

2.12.2 This issue arose in many European member states, therefore Directive 75/318/EEC formally required that all medicines that were on the market in member states prior to 22 November 1976 had to be reviewed for quality, safety and efficacy. These reviews had to be completed by 20 May 1990.

2.12.3 In the UK the Committee for the Review of Medicines was established in 1975[10] to carry out reviews of UK PLRs. The CRM was initially faced with almost 40,000 PLRs, however the vast majority of these were never converted to full licences either because the manufacturer let the licence lapse, or the LA revoked or suspended the PLR. Just over 6,000 PLRs were

[8] https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:31965L0065&from=EN
[9] Section 6 of the Medicines Act 1968
[10] SI 1975/1066

considered for conversion to full licences. In 1992 after it had completed its work the CRM was formally dissolved.[11]

2.13. The Medicines Control Agency

2.13.1 During the 1980s the Medicines Division frequently breached the product licence application timelines laid down by the EU, by the mid to late 1980s serious concerns were raised about the ability of the Medicines Division to cope. In response the Secretary of State for Social Services set up what became known as the Evans-Cunliffe Inquiry. The pharmaceutical industry and other interested parties contributed to the inquiry and Evans-Cunliffe report was released in December 1987.[12] The 1987 Report recommended the reorganisation and restructuring of UK pharmaceutical regulation, including a shift from the existing part industry/part governmental funded model to model were the funding came solely from the pharmaceutical industry.

2.13.2 In 1988 the Department of Health and Social Services was split into two Departments, Health and Social Services. On 1 April 1989 the Medicines Division was spun out of the Department of Health to become the Medicines Control Agency (MCA). The MCA was funded by fees for the processing of licences, and in 1991 it became an executive agency of the Department of Health, giving more financial freedom.

2.14. The Medicines and Healthcare Products Regulatory Agency

2.14.1 There was considerable criticism of the Medicines Control Agency for not being sufficiently effective, visible and transparent. This culminated in a critical report by the Public Accounts Committee[13] then from 1 April 1989 to the Medicines Control Agency, which merged with the Medical Devices Agency on 1 April 2003 to form the Medicines and Healthcare Regulatory Agency (MHRA).

2.15. EU Medicines Regulation Organisations

2.15.1 The European Medicines Agency (EMA) is responsible for human and animal medicinal products, including evaluating quality and efficacy, oversight of pharmacovigilance for pharmaceuticals, producing scientific advice and safety evaluations as well as more specialist

[11] SI 1992/606
[12] Evans N.J.B & Cunliffe P.W. *Report on the Study on the Control of Medicines*. 1987 DHSS
[13] PASC *Safety, Quality, Efficacy: Regulating Medicines in the UK* (**HC:** 255 2002-2003, January 16, 2003) available at https://www.nao.org.uk/report/safety-quality-efficacy-regulating-medicines-in-the-uk/

functions including paediatric investigation plans, designating 'orphan' status and assignment to small or medium sized enterprises.

2.15.2 The EMA is assisted by seven committees, which provide expert scientific input and opinions in their designated areas, Figure H.5

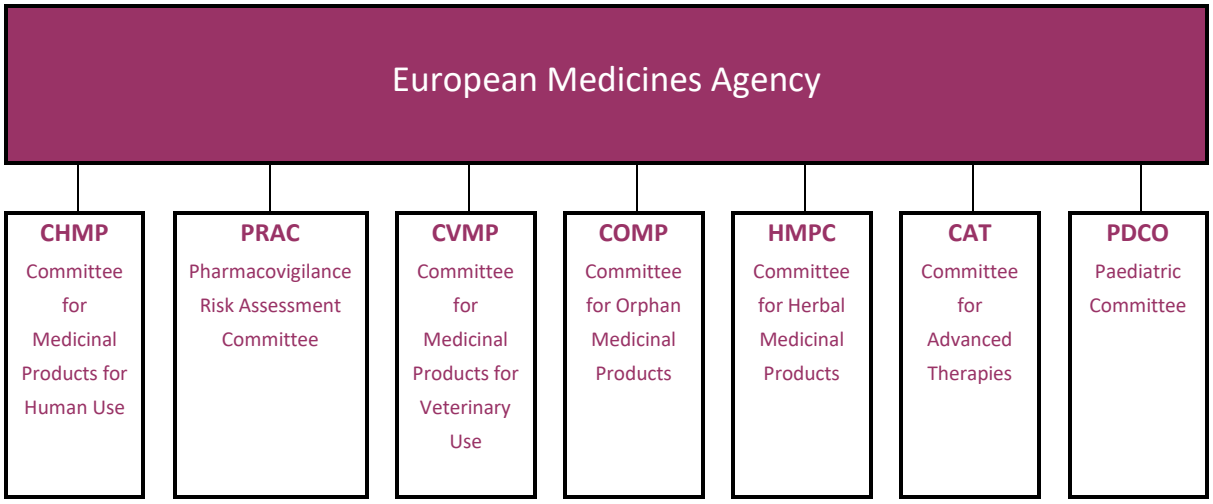

Figure H.5 Committees of the European Medicines Agency

2.15.3 The EMA provides the secretariat and co-ordinates these committees. Each committee has members from each EU member state. The chair and deputy chair are elected by committee members for a fixed term.

2.16. Current EU regulatory requirements for pharmaceuticals

2.16.1 Pharmaceutical regulation in the EU has evolved considerably since the UK's accession. A full description of all of the changes will not be detailed here, relevant details will be briefly highlighted to provide context.

2.16.2 Product development. The individuals, the facilities, the conduct of experiments and the way in which animal are used[14] are all regulated under EU law.[15]

2.16.3 Premarketing testing. All pharmaceuticals placed on the European market have to undergo pre-marketing safety tests in the form of Clinical Trials, which are approved by the relevant

[14] Directive (EEC) 86/609; the Animals (Scientific Procedures) Act 1986.
[15] 'GLP': Directives (EC) 2004/10 and (EC) 2004/9.

Member State. Clinical Trials must be registered with the European Medicines Agency.[16] They are divided into three phases, see Figure H.6.

Phase	Approximate Test population	Objective
I	20-100 health volunteers	Safety check & look for efficacy
II	100-300 patients with the target disease	Safety check & establish efficacy
III	300-3,000 patients with the target disease	Safety check & establish therapeutic effect

Figure H.6 Clinical trial phases

2.16.4 Marketing authorization. A pharmaceutical cannot be place on the market in any EU member state until it has a valid marketing authorization. An application for marketing authorization has to be in a prescribed form and must contain certain information. There are two ways to obtain a marketing authorization.

2.16.5 Centralised market approval. Under the centralised route the medicine is licenced by the EMA and this automatically applies across all EU states. Certain classes of drugs have to use the centralised route.

2.16.6 Decentralised market approval. The decentralised route, also known as mutual recognition, involves a national Competent Authorities licensing the medicine. Any other National Competent Authority can then be asked to recognise the marketing authorization held in the first state and to automatically grant a national marketing authorization based on this.

2.16.7 Decentralised market approval creates a 'market place' for national competent authorities. Based on population size the MHRA has traditionally held a disproportionately large share of the market approvals granted in the EU.

2.16.8 Post-marketing pharmacovigilance. As the number of individuals involved in pre-clinical testing is relatively small not all side effects and adverse drug reactions will be detected at the pre-clinical stages. Post-marketing pharmacovigilance is used to detect and monitor side effects and adverse drug reactions that occur in normal everyday use.

2.16.9 A 'signal' is new association or a new aspect of a known association between a drug and an adverse event.

2.17. Adverse Event Report in the UK

[16] https://www.clinicaltrialsregister.eu

2.17.1 The UK was one of the first countries to develop a drug adverse event reporting system. The Yellow Card system (named after the postage-paid yellow cards sent to doctors to report Adverse Drug events to the authorities, initially the CSD) began in May 1964. From 1997, reports were also accepted from pharmacists. In 2002, the Yellow Card Scheme was extended so that nurses, midwives and health visitors could also report suspected ADRs. and continues to date. It was updated to incorporate patient reports from January 2005[17] and now has an app which is live across six EU countries.

2.18. Pharmacovigilance in the EU

2.18.1 Post-marketing surveillance, or pharmacovigilance, is mandated under EU law; with specified obligations placed on Member States, the Commission, the EMA, the CHMP,[18] the marketing authorization holders, the manufacturing authorizations holders and the holders of wholesale distribution authorizations. In the UK pharmacovigilance follows Standard Operating Procedures which apply the EMA Practice Guidelines.

2.18.2 The EU pharmacovigilance system relies heavily upon spontaneous reporting of adverse reactions.[19] Since 2005 the format of, and terminology used in, suspected adverse drug event reports to EU Regulators have been standardised.[20]

2.18.3 Yellow Card reports feed into a broader EU-wide system - the Eudravigiliance database. The Eudravigilance database contains suspected ADRs reports for medicines that are authorized or in clinical trials in the EEA, these reports can come from all over the world.

2.18.4 Pharmacovigilance in the EU works on a collaborative assessment and data sharing across the EU network. Competent Authorities and the EMA each monitor a designated set of pharmaceutical substances. They assess electronic Reaction Monitoring Reports (eRMRs) from the Eudravigilance database to identify any concerns about their designated medicines.

2.18.5 Electronic Reaction Monitoring Reports from Medicines that need additional monitoring medicines are examined twice a month. Established medicines' eRMRs are checked on a

[17] Avery, A.J., et al., *Evaluation of patient reporting of adverse drug reactions to the UK 'Yellow Card Scheme': literature review, descriptive and qualitative analyses, and questionnaire surveys.* Health Technol Assess, 2011. **15**(20): p. 1-234, iii-iv.

[18] Centralised system: Regulation (EC) 726/2004, Art 25. Decentralised system:

[19] Directive (EC) 2001/83, Art 102, as amended: adapted from its first introduction in Directive (EEC) 93/39, Art 3(3).

[20] The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

monthly basis. All member states can access to reports for any substance not just their own designated products.

2.18.6 All reports from Eudravigilance are entered into the WHO global pharmacovigilance database VigiBase.[21] UK access to VigiBase continues irrespective of EU membership.

2.19. Referrals to the EMA

2.19.1 If a member state has a concern about a medicinal product, then they can make a referral to the EMA to examine the issue. Referrals can be made under various different regulations depending upon the question at hand.

2.19.2 Scientific Opinions. The procedure under Article 5(3) of Regulation (EC) No 726/2004 is used to ask the CHMP to give a scientific opinion. Adoption of Scientific opinions usually requires a quorum (achieved when two thirds of voting committee members present) and either a consensus or a majority vote in favour. At the CHMP meetings the views and opinions of the CHMP members are exchanged and co-ordinated and where possible an inclusive CHMP opinion is reached based on consensus. If a consensus cannot be reached a vote is required. Two such referrals have been made for Hormone Pregnancy Tests in 2018[22] and 2019.[23]

2.19.3 In the EMA policy on Conflicts of Interest for Scientific Committees[24] interests are classified into three categories.[25] Direct Interests, Indirect interests and Other interests. Direct and Indirect interests end when the relevant party stops receiving money. Other interests are subject to a cooling off period, in most cases three years, though this is adapted to reflect the individual circumstances. If the Chair of a Committee, such as the CHMP, has any declared interest in a product or company there are very limited circumstances in which they can participate in medicinal product related committee matters.[26]

[21] https://www.who-umc.org/vigibase/vigibase/
[22] https://www.ema.europa.eu/en/documents/minutes/minutes-chmp-meeting-28-31-may-2018_en.pdf
[23] https://www.ema.europa.eu/en/documents/minutes/minutes-chmp-meeting-10-13-december-2018_en.pdf
[24] https://www.ema.europa.eu/en/documents/other/policy-44-european-medicines-agency-policy-handling-competing-interests-scientific-committees_en.pdf
[25] See section 4.2.1.1 *ibid*
[26] See annex 1 *ibid*

2.19.4 Pharmacovigilance. Questions related to data generated by pharmacovigilance may lead to an Article 31 referral. These can concern a wide range of aspects of how a medicine is prescribed, used and monitored.

2.19.5 Referrals under Article 31 of Directive 2001/83/EC are initially carried out by PRAC. As valproate medicines in the EU are all authorised nationally, the PRAC recommendations were forwarded to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) for a position. The CMDh, a body representing EU Member States, is responsible for ensuring harmonised safety standards across the EU for medicines authorised via national procedures. There have been two Article 31 referrals for Valproate in 2014 and 2017, which resulted in the Pregnancy Prevention Programme (PPP).

3. Medical devices

3.1. 3.1 Background

3.1.1 The regulation of Medical devices is separate from the regulation of medicines and has a different regulatory structure and set of requirements for marketing authorisation. A brief history will be outlined for context rather than a detailed description.[27]

3.2. UK Medical Device regulation up to and including the 1950s

3.2.1 During the Second World War the Directorate of Medical Supplies, a part of the Ministry of Supply, ensured the supply of medical equipment (devices) by encouraging UK manufacturing. In 1947 responsibility for the procurement of medical supplies for public services passed to the Ministry of Health. The expertise within the Directorate of Medical supplies became the Technical Services Group within the Ministry of Health, whose role included inspecting and testing medical equipment.

3.3. Early Medical Devices Regulation 1960s

[27] For a fuller history see Jefferys, D.B., *The regulation of medical devices and the role of the Medical Devices Agency.* Br J Clin Pharmacol, 2001. **52**(3): p. 229-35.,

3.3.1 The 1960s saw rapid expansion in the types, complexity and availability of medical devices. Suggestions to include medical device regulation within the 1968 Medicines Act were not taken up.[28] In 1969 three steps were taken assure quality and safety

- The Scientific and Technical Board (STB) of the Department of Health was created,
- The defect and adverse incident reporting system was created, and
- a voluntary quality assurance system for manufacturers covering design and production and incorporating compliance inspections was also launched.

3.4. Voluntary quality assurance scheme and the Manufacturers Registration Scheme (MRS)

3.4.1 The voluntary quality assurance system for manufacturers was a forerunner scheme which evolved into the Manufacturers Registration Scheme (MRS). The MRS was voluntary, but compliance with the quality assurance element was needed to sell devices to the NHS. This ensured that the scheme had a high uptake with almost 600 worldwide manufacturing sites registered. The Manufacturers Registration scheme closed on 14 June 1998 when the transitional period of the Medical Device Directive 93/42/EEC ended.

3.5. The Scientific and Technical Board (STB) of the Department of Health, the Medical Devices Directive (MDD) of the Department of Health and the Medical Devices Agency (MDA)

3.5.1 Starting in the 1980s the STB underwent several changes, initially being incorporated into the NHS Procurement Directorate. This entity was then separated into the NHS Supplies Authority and the Medical Devices Directorate (MDD).[29]

3.5.2 In September 1994 the MDD was renamed the Medical Devices Agency and was spun out as an Executive Agency of the Department of Health. The main aim of the MDA was to protect public health and safeguard the interest of patients and users by ensuring that medical devices and equipment met appropriate standards of safety, quality and performance and that they complied with relevant Directives of the European Union.

3.6. The UK Medical Devices Evaluation Program

[28] MH168/15 Letter from S.M. Davies to Mr Hulme dated March 1968 and associated suggested amendments to the Medicines Bill (which would become the Medicines Act 1968)
[29] *ibid*

3.6.1 Interestingly as well as running the Manufacturers Registration Scheme the STB also ran the medical device evaluation programme which provided the NHS with advice about the safety and performance of the medical devices. This evaluation programme continued to be run by the MDA until 2005 when it was moved into the Centre for Evidence based purchasing within the NHS Purchasing and Supplies Agency as part of the reorganisations recommended by the HealthCare Industries Task Force.[30]

3.6.2 Subsequently SERNIP and then NICE took on responsibility for evaluating certain devices.

3.7. The UK Committee on the Safety of Devices

3.7.1 In 2001 the Committee on the Safety of Devices was set up to advise the MDA. This was a non-statutory body, which relied upon around 40 expert clinician who were not reimbursed for their contribution. The remit of the Committee on Safety of Devices was to support the MDA by giving advice on a range of device related initiatives.

3.7.2 In 2012 Professor Terence Stephenson undertook an independent review on MHRA access to clinical advice and engagement with the clinical community in relation to medical devices.[31] This was, in part, prompted by high profile events such as the PIP breast implants fraud,[32] metal-on-metal hips, and mesh used for vaginal Pelvic Organ Prolapse (POP)[33] repair, as well as other structural reorganisations of the NHS and the wider health and regulatory systems. Professor Stephenson made 12 key recommendations, see Figure H.7, including recommendation 1 which advocated creating a formal mechanism for clinical input to MHRA on devices. This was achieved by replacing the Committee on the Safety of Devices with the Devices Expert Advisory Committee.

[30] Wilkinson, J., *Task force recommendations to transform UK industry.* Med Device Technol, 2004. **15**(10): p. 36-7.
[31] Stephenson T. Independent review on MHRA access to clinical advice and engagement with the clinical community in relation to medical devices. (2013) available at https://www.pmguk.co.uk/data/page_files/publications%20and%20reports/2014/con402542.pdf
[32] https://www.nhs.uk/conditions/pip-implants/
[33] See Chapter 5 Pelvic Mesh for further detail.

3.8. Devices Expert Advisory Committee (DEAC)

3.8.1 The DEAC[34] is a voluntary, non-statutory committee that provides support to the MHRA - in the following six areas:- Devices Strategy; Communication; Professional Networking; Quality Assurance; Professional advice; e-Health.

Key Recommendations of Professor Terence Stephenson

Organisation of clinical advice input, resources and leadership

1 The MHRA must take devices as seriously as medicines: Create a formal mechanism for clinical advice input to MHRA.

2 Review the MHRA resources needed.

3 Ensure that adequate clinically trained staff are included in the MHRA staff.

4 Develop and manage the network of clinical advisors.

5 Develop the existing collaboration with EU bodies with similar aims to the UK MHRA.

Collecting and using device incident data

6 Build links with the Clinical Commissioning Groups to help improve the flow of information on safety and performance of devices.

7 Improve and simplify the way incidents are reported, aiming to obtain reports on all device incidents.

8 Develop means by which devices implanted in patients can be identified by their Unique Device Identifiers, and means by which patients with specific devices can be traced.

Communications and partnerships

9 Improve communication about adverse incidents to patients and the public, clinical staff, clinical scientists, hospital managers and professional bodies.

10 Develop improved communications about the MHRA's role in ensuring the safety of devices with clinicians, clinical scientists, hospital managers and the public.

11 Develop collaboration with relevant English bodies, including NICE, NHS organisations, Public Health England, with the UK Academy of Medical Royal Colleges and also with devolved administrations.

Future developments and emerging challenges

12 Support the safe introduction of new and innovative technologies into clinical practice.

Figure H.7 Key Recommendations of Professor Terence Stephenson

[34] https://www.gov.uk/government/groups/devices-expert-advisory-committee

3.9. European Regulation of Medical Devices

3.9.1 Medicines had had specific legislation and provisions since the inception of the EU, but Medical Devices followed much later.

3.9.2 In 1993 the first EU regulations systematically governing the marketing of medical devices in the EU were devised,[35] and these were mandatory from mid-June 1998. The first European Medical Device specific legislation was known as the 'New Approach'. Under the 'New Approach' every single medical device, even the lowest risk ones such as plasters, had to meet the 'essential requirements', with more stringent regulatory requirements for higher risk devices.

3.9.3 European legislation is currently in transition and a new set of requirements, the Medical Devices Regulation,[36] were due to be fully in force from May 2020, but due to COVID-19 This has been delayed until May 2021. Among other things the new regulations change the way in which devices will be assessed prior to marketing. The delay in implementing the MDR means that, as it currently stands, the MDD will be in force at the end of the transition period for the UK leaving the EU.

3.9.4 The 'New Approach' was contained within three directives:

- the Active Implantable Medical Devices Directive (90/385/EEC) which covered active implantable devices such as pacemakers
- the Medical Devices Directive (93/42/EEC) which covered all other devices except in vitro diagnostic devices
- the In Vitro Diagnostics Directive (98/79/EEC) which covered in vitro diagnostics.

3.9.5 Pelvic mesh products fall under the Medical Device Directive, so this review will focus on that legislation.

3.9.6 The Medical Devices Directive 93/42/EEC became applicable from 1 January 1995, with a transitional period until 14 June 1998. During the transitional period a Medical Device could be marketed in the EU either in accordance with the pre-existing national rules or in compliance with the Directive.

[35] Directive 93/42/EEC had a transitional period between 1/1/95 and 14/06/1998 after which it was in force.
[36] Medical Devices Regulation, Regulation 2017/745 available at https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:02017R0745-20170505

3.9.7 The Medical Devices Directive 93/42/EEC laid out the conditions required to market a medical device within the EU, including requirements for Competent Authorities and Notified Bodies.

3.10. Device Classes

3.10.1 Medical devices cover everything from plasters to complex implantable devices, such as pacemakers. Therefore, there are different requirements for CE marking according to the potential risk posed by the device.

3.10.2 Devices are classified as follows.[4]

- **Class I – lowest risk** – non-invasive device, do not interact with the body, e.g. plasters, bed pans
- **Class IIa – medium risk** – limited to interacting with natural orifices, may involve power, e.g. hearing aids, powered wheelchairs
- **Class IIb – medium risk** – most surgically active devices - partially or totally implantable - may involve altering bodily fluid composition, e.g. surgical lasers, ventilators
- **Class III – high risk** – devices that support/sustain life, significantly prevent health impairment or have high potential to cause illness/injury. All devices that connect directly to the circulatory system or CNS and/or contain a medicine, e.g. heart valves, breast implants.

3.10.3 Mesh for both SUI and POP were class IIb, but will move up to class III with the advent of new regulations.

3.11. CE mark

3.11.1 In order to be lawfully put on the EU market a medical device must obtain a CE mark, certifying that it complies with the requirements of the Directive.

3.11.2 Once a medical device has a CE mark it may be freely placed on the market across the EU in any member state without any further restrictions or requirements.

3.11.3 The EU has a decentralised certification system for medical devices marketing. The CE marking procedure varies according to the Class a device is put into.

3.11.4 Manufacturers can self-certify most Class I devices. They affix a CE mark and register the device with the national competent authority where it is being sold. This means that the Competent authority is aware of all the low risk devices on the market in that country.

3.11.5 Class II and III device certification requires the involvement of a Notified Body.

3.11.6 Certifying class III devices requires the highest level of scrutiny, with a Notified Body required to assess the quality system. This involves looking at the premarket testing, the clinical investigations the manufacturing process and the post-marketing vigilance systems.

3.12. Competent Authorities

3.12.1 Although they share a name the function of Competent Authority for medical devices differs from the function of a Competent Authority for medicines. This is because medical devices are certified not licensed.

3.12.2 Each member state has one national Competent Authority which is responsible for supervising, auditing and designating the Notified bodies within their country.

3.12.3 In the UK the Competent Authority was the Medical Devices Agency until 2003, when the MDA merged with the MCA to form the MHRA.

3.12.4 The Competent Authority is also responsible for specified elements of post-marketing vigilance and enforcement actions.

3.13. Notified Bodies

3.13.1 There is no set structure for a Notified body, they can be private, state run, commercial or not for profit. There is no fixed number of Notified Bodies within an EU state; this is for the national Competent Authority to determine.

3.13.2 Notified bodies check that the device complies with the requirements of the Medical Devices Directive (MDD).

3.13.3 Under the MDD the level of involvement that a Notified Body has in the certification process depends upon the class of the device being certified, see Figure H.8. Higher risk devices require a higher level of Notified Body involvement.

	Product certification			Quality system assessment	
	Design examination certificate	Type examination certificate	Certificate of Conformity	Certificate of Full Quality Assurance System	Certificate of Production Quality Assurance
	Annex II(4)	Annex III	Annex IV	Annex II(3)	Annexes IV(3) & VI(3)
Class I					
Class IIa			X	X	X
Class IIb		X	X	X	X
Class III	X	X	X	X	X (Annex IV(3) only)

Figure H.8 Notified Body involvement required for different medical device classes

3.14. Certification by Notified Bodies

3.14.1 Devices are generally assessed by Notified Bodies in one of two ways. One option is using an individualized product assessment tailored to that specific device. Another option is to assess the device against harmonised standards detailing the design, testing and marketing requirements as per the MDD and ISO 9000 standards[37] as customised for medical devices by EN 46000.[38]

3.14.2 Harmonised standards exist for various aspects of medical devices, some of which are listed in Figure H.9.

Number	Aspects covered
EN 13485	Medical Devices quality management systems – regulatory system requirements
EN 1041	Information and labelling for medical devices
EN 980	Graphic symbols
EN 10993 series	Biological evaluation of medical devices

[37] ISO 9000 is a set of international standards on quality management and quality assurance developed to help companies effectively document the quality system elements needed to maintain an efficient quality system.
[38] EN 46000, the Medical Device Quality Management Systems Standard, customises the implementing ISO 9000 for the particular concerns of the medical devices industry. Published in 1994 EN 46000 embraces the principles of good manufacturing practice, commonly used in medical device manufacture. It offers its users an auditing process similar to a quality management systems audit.

EN 14155-1 and -2	Clinical investigation of medical devices for human subjects. Part 1 covers general requirements, part 2 covers clinical investigation plans
EN 60601 series	Medical electrical equipment
EN 14971	Application of risk management to medical devices.

Figure H.9 Harmonised standards for medical devices

3.14.3 Of particular interest for pelvic mesh is the ISO 10993 series, which covers biocompatibility.

3.14.4 Since 1998 the Medical Devices Directive has required either clinical investigations or clinical evaluations before an implantable device can be CE marked. Clinical investigations are scientific and clinical testing of how a device will perform when it is implanted and have to be carried out according to conditions laid out in the MDD. Clinical evaluation reports consist a review of the published literature on clinical experience with that device or with a similar equivalent device that is already in use. If the clinical evidence comes from experience with a device already in use (a predicate device) then the clinical evaluation report includes a statement on how their device is equivalent to the predicate device.

3.14.5 The Medical Devices Directive[39] does not define 'equivalent'. The interpretation of equivalence rested with the notified body, aided by guidance issued by the EU and national competent authorities.[40] There are examples of CE marked devices claiming equivalence to a device made from a totally different material, or a claiming equivalence to a device that has the same function, but is implanted in a different way. There was also no requirement that the predicate device had to be CE marked or used/sold in the EU, for example, Ethicon's market leading TVT certification included equivalence to Boston Scientific's ProtoGen sling, despite fact that the ProtoGen was not CE marked and sold in the EU. If a predicate device is withdrawn for safety reasons, as the ProtoGen sling was in 1999, there is no automatic recall of daughter devices. The onus is on the manufacturer and notified body to monitor their device for safety issues. Indeed, there is no centralised way to trace daughter devices that stem from a common predicate device; the only people who know which device was used as a predicate are the manufacturer and the notified body.

3.14.6 Under the new Regulation certification based on equivalence has more stringent requirements, the predicate device has to be CE marked, the materials used have to be the same, the manufacturer has to have access to the full design dossier of the predicate device. Obtaining a design dossier will be straightforward for manufacturers updating the design of

[39] 93/42/EEC

[40] For example, the various revisions of MEDDEV 2.7/1 and the MHRA, *Guidance Notes for Manufacturers on Clinical Investigations to be carried out in the UK* (2008).

one of their existing products. However, concerns have been raised that it will be more difficult for manufacturers updating a competitor's device to obtain that design dossier, and that this might stifle innovation.

3.14.7 The new regulations bring in more rigorous requirements for clinical investigation for high risk devices. For class III devices (includes mesh), manufacturers must produce a summary of safety and clinical performance (SSCP). The SSCP summarises the device safety and performance and the outcome of the clinical evaluation. The SSCP must be validated by the NB responsible for the conformity assessment. The SSPC must be publicly available.

3.15. Adverse Device Reports

3.15.1 Reporting requirements under the new Medical Device Regulations are more stringent. Manufacturers must report any serious incidents and unexpected trends in adverse events.

Incident type	Timeframe for reporting
Serious incident	Immediately after the manufacturer has established the causal relationship between that incident and its device, or that such causal relationship is reasonably possible, and not later than 15 days after it becomes aware of the incident.
Serious public health threat	Immediately, and not later than 2 days after the manufacturer becomes aware of that threat.
Death or an unanticipated serious deterioration in an individual's state of health	Immediately after the manufacturer has established or as soon as it suspects a causal relationship between the device and the serious incident, but not later than 10 days after the date on which the manufacturer becomes aware of the serious incident.

Figure H.10 Medical device manufacturer reporting requirements by incident type

3.15.2 The vigilance reporting timescales are described in Annex 87 of the Regulations and are summarised in

3.15.3 Figure H.10. The question of what events should be reported is considered in Chapter 5 Pelvic mesh at paragraph 5.110.

3.15.4 The Regulations are clear that reports must be submitted electronically, and in order to meet the deadlines a manufacturer may submit an incomplete initial report, which must be followed by a complete report.

3.15.5 Trend reporting of other adverse events is detailed at Article 88 of the 2017 Regulation. Briefly manufacturers must report any statistically significant increase in the frequency or severity of incidents that are:
(a) not serious incidents; or
(b) expected undesirable side-effects that could have a significant impact on the benefit–risk analysis and which have led or may lead to risks to the health or safety of patients, users or other persons that are unacceptable when weighed against the intended benefits.

3.15.6 The significant increase is measured relative to the foreseeable frequency or severity of such incidents that is detailed in the technical documentation and product information.

3.16. EUDAMED in the EU

3.16.1 There is currently no centralised database of medical devices marketed across the EU. In the EU the EUDAMED database is being developed to remedy this.

3.16.2 EUDAMED[41] is an information system for exchanging legal information related to the application of European Union Directives on medical devices between the European Commission's Enterprise and Industry Directorate General and the Competent Authorities in the European Union Member States.

3.16.3 There will be a vigilance modules on EUDAMED which will be searchable to an appropriate degree by the public need, further guidance is expected on what is an ‘appropriate degree’.

3.16.4 The EUDAMED database was due to be up and running in May 2020. However, this will not be the case and the MDR contains provisions to deal with a delay to launch. It seems unlikely that EUDAMED will launch while the UK still adheres to EU rules as part of the transitional arrangements which finish at the end of 2020.

[41] https://ec.europa.eu/growth/sectors/medical-devices/new-regulations/eudamed_en

3.17. The contrast between EU and US device databases.

3.17.1 In contrast to the EU the FDA in America has a centralised system. A device can be brought to market via one of two routes, approval or clearance. Some classes of device have to be approved rather than cleared. Some devices are exempt from requiring either approval or clearance. [42]

3.17.2 Approval. This involves the FDA considering an application made using the Pre-market approval (PMA) process and approving a device base on the statutory required elements.[43] Devices approved using this route are entered into the PMA database, a publicly accessible and searchable database.[44]

3.17.3 Clearance. In the US devices can also be cleared for sale using the 510k process. The FDA do not approve these devices, they are notified by the manufacturer that the product will be placed on the market based on equivalance. Clearance is based on showing 'substantial equivalence' to a device that is already on the market. Devices cleared for sale using this route are entered into the 510k database, a publicly accessible and searchable database.[45]

3.17.4 Adverse Device Reports. The FDA has a device reports database, MAUDE.[46] MAUDE is the Manufacturer and User Facility Device Experience, a database of adverse events reported to the FDA. MAUDE is publicly accessible. Until June 2019 there are some adverse events that are not reported to MAUDE, but were reported via a mechanism called alternate summary reporting. Alternative Summary Reports could include serious injuries and malfunctions, but not patient deaths or unusual/uncommon adverse events. Alternative Summary reports were made quarterly by manufacturers to the FDA but were not accessible by the public, leading to criticism. Alternate summary reporting ceased in June 2019.

3.17.5 The FDA also hold the Global Unique Device Identifier Database, GUDID.[47] This holds a publicly searchable Unique Device Identifier (UDI) information. It is effectively a reference catalogue for each device, containing device identification information, such as the device

[42] See Chapter 2 *The Regulation of Medicines and Medical Devices*; part F. *US Regulation of Medical Devices* in Macleod S and Chakraborty S *Pharmaceutical and Medical Device Safety: A study in Public and Private Regulation* (Hart, 2019)
[43] Title 21 of the Code of Federal Regulations part 814.20
[44] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm
[45] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm
[46] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm
[47] https://accessgudid.nlm.nih.gov/about-gudid

identifier on the label, device name, company name, MR safety status, and premarket submission numbers.

4. Service provision, cost, effectiveness and value for money

4.1. The National Health Service

4.1.1 Since the inception of the NHS there have been concerns about the cost, effectiveness and value for money of treatments. This report only details the agencies relevant to the interventions under review, so does not provide comprehensive coverage.

4.2. The Joint Standing Committee on the Classification of Proprietary Preparations

4.2.1 The Joint Standing Committee on the Classification of Proprietary Preparations (known as the MacGregor Committee[48] between 1965 and 1971) provided guidance as to which preparations should be used on the NHS.

4.2.2 At the time that the adverse events were reported from the Hormonal Pregnancy Tests the Joint Standing Committee on the Classification of Proprietary Preparations' terms of reference were: [49]

i. To advise on the classification of proprietary pharmaceutical preparations with the object of helping doctors to decide which should be used in the treatment of their patients, and to identify those preparations the prescribing of which appears to call for special justification.

ii. To keep under review the principles for determining whether preparations should properly be regarded as drugs, foods, toilet preparations or disinfectants and to give advice on the classification of particular preparations submitted to the Committee.

4.2.3 The MacGregor Committee stated that they took into account relative efficacy together with relative toxicity in order to make recommendations to help doctors decide which

[48] Named after its chair Prof Alistair MacGregor who chaired it between May 1965-August 1971, prior to this it was chaired by Lord Cohen between its creation in 1949 and April 1965.
[49] New Drug Classification: Statement of Principles by New Committee BMJ 15 May 1965: 1306

preparations should be used. It is clear that they considered the safety of a preparation as well as it's efficacy.

4.2.4 The MacGregor Committee published the PropList from April 1967 with the eighth edition published in February 1970.[50] The Final edition was the June 1970 supplement to the 8th Edition. The Proplist categorised drugs into the following categories described in Figure H.11.

Category	Definition
Monograph preparations	
Mon (A)	Acceptable preparations whose active therapeutic constituents are identical with those of preparations described in the British Pharmacopoeia, British Pharmaceutical Codex or British National Formulary or which differ only slightly in physical form from such standard preparations, the different being such as to have little or no therapeutic significance.
Mon (B)	Preparations whose active therapeutic constituents are identical with those of preparations described in the British Pharmacopoeia, British Pharmaceutical Codex or British National Formulary or which differ only slightly in physical form from such standard preparations and whose administration the Committee would regard as unacceptable because:- (a) They are of greater toxicity or lesser efficacy than alternative preparations or (b) Their use does not necessarily represent good therapeutic practice or (c) They are mixtures of drugs, the administration of which the Committee regards as open to question
4.2.5 Category A sub-divided into:-	
Category A.1	Preparations of single therapeutically active drugs which are acceptable formations of substances (or active constituents of preparations) in the British Pharmacopoeia, British Pharmaceutical Codex or British National Formulary.
Category A.2	Preparations of single therapeutically active drugs which have been shown to the Committee's satisfaction to have an acceptable degree of efficacy in relations to their toxicity and therapeutic indications

[50] Standing Joint Committee on the Classification of Proprietary Preparations. *PropList*. VIII ed. Feb 1970

	and which in the light of alternative available preparations can be recommended for use.
Category A.3	Acceptable preparations containing more than one drug where the main components are the active ingredients in Categories Mon (A), A.1 or A.2.
Category B sub-divided into:-	
Category B.1	Preparations which, in the opinion of the Committee, on the evidence produced to it, have an unacceptable lesser degree of efficacy or are of an unacceptably greater toxicity than alternative preparations in Categories Mon (A) or (A). Also preparations containing mixtures of drugs which may individually have some degree of therapeutic efficacy but where the Committee would regard the administration of such a mixture as open to question.
Category B.2	Unacceptable preparations which consist of or contain drugs which, in the view of the Committee, are not of proven efficacy.

Figure H.11 PropList classification categories

4.2.6 The Committee recommended that preparations in Categories Mon (A), A.1, A.2 and A.3 should be provided on prescription by the NHS. Although there were no restrictions on what drugs a doctor could prescribe if he considered them necessary for the treatment of his patients, the Committee felt that the prescribing of Category B preparations might require special justification if the doctor's prescribing were being formally investigated.

4.2.7 The Category B section of the Proplist, essentially indicated that the medicine should not be used as a primary treatment option. As the UK had a National Health Service which dominated the healthcare market, the financial impact of classifying a product in Category B was potentially substantial for manufacturers.

4.2.8 The PropList was sent to all prescribers free of charge. However, compliance with PropList recommendations relied upon the prescriber checked the PropList when prescribing. The VIII Edition of the PropList states that when determining the classification the Committee took into account the indications for which a product was promoted, but that it was the responsibility of the prescriber to check the indication he is prescribing the drug for is one for which efficacy has been proven.

4.2.9 There was evidence this was not a very effective mechanism for controlling prescribing. For example, the PropList recommended that generic medicines were used in place of more

expensive branded medicines, as it was clear this was not happening recommendations were made to allow pharmacists to make generic substitutions when dispensing.[51]

4.2.10 The MacGregor Committee was disbanded in October 1970.[52]

4.3. Subcommittee on Pregnancy Diagnostic Tests

4.3.1 The Subcommittee on Pregnancy Diagnostic Tests was a subcommittee of the DHSS' Central Pathology Committee. During 1966 the subcommittee discussed the provision of various immunological methods pregnancy testing by the NHS and the reimbursement of hormone pregnancy tests by the NHS. These discussions included gathering expert advice on the safety, reliability and cost of HPTs, see Annex E HPT supporting information for further details.

4.3.2 In 1966 the Subcommittee on Pregnancy Diagnostic Tests recommended phasing out Hogben tests and replacing it with immunoassays. Two immunoassays were placed on the Central Supply list from 1 February 1967,[53] and arrangement were put in place for these test to be carried out in hospital pathology labs at the request of GPs.[54]

4.4. The 1993 Advisory Council on Science & Technology Report

4.4.1 In the 1990s it was recognised that there were difficulties in balancing cost-effective prescribing and access to new innovative treatments. For example, in 1990 62% of the total spend on medicines was for medications that were approved before 1970.[55]

[51] Informal Working Group on Effective Prescribing. *Report to the Secretary of State for Social Services. (Greenfield Report)*. 1983. , Department for Health and Social Security: London
[52] *Classification of proprietary preparations.* Lancet, 1970. **2**(7678): p. 286; *Death of proplist.* Lancet, 1970. **2**(7679): p. 918
[53] The documents in the file record two start dates, 1 January and 1 February. Other contemporaneous documents indicate that the services were not in place on 1 January.
[54] MH 149_1105 page 3
[55] Griffin, J.P., *'Is Therapeutic Conservatism Cost Effective Prescribing?'* EFPLA General Assembly, Salzburg, May 1993 page 1.

4.4.2 The 1993 Advisory Council on Science and Technology report *'A Report on Medical Research and Health'* provided some key recommendations for reforms both for devices and for medicines.[56]

4.5. Safety and Efficacy Register for New Interventional Procedures (SERNIP)

4.5.1 Department of Health was advised in the 1993 Advisory Council report to set up *'a committee on safety and efficacy of procedures to review and register novel surgical procedures'* with statutory powers similar to the Committee on Safety of Medicines. They did not, instead they opted for a voluntary organisation, the Safety and Efficacy Register for New Interventional Procedures (SERNIP), hosted by the Standing Committee of Medical Royal Colleges. SERNIP made recommendations, but had no enforcement powers and was widely regarded as underfunded and not independent.

4.5.2 On 1 April 2002 SERNIP's responsibilities were formally handed over to the National Institute for Health and Clinical Excellence (NICE).

4.6. National Institute for Health and Clinical Excellence (NICE)

4.6.1 The 1993 Advisory Council on Science and Technology report found 'that innovations, which are recognised as offering significant economic and/or quality of life advantages should be fully funded by the NHS.'. In 1997 the government put forward a white paper proposing NICE.[57] NICE was set up in April 1999 as a Special Health Authority with the aims of improving patient standards of care and reducing inequalities in access to treatments, so called 'postcode prescribing'.

4.6.2 NICE produces guidance on the cost effectiveness of interventions for the NHS in England and Wales. NICE was set up to be advisory. The equivalent function in Scotland is carried out by the Scottish Medicines Consortium (SMC).

4.6.3 NICE produce several types of guidance with differing legal implications for the NHS.

[56] Advisory Council on Science and Technology. *A report on medical research and health*. London: Office of Science and Technology, HMSO 1993;28
[57] Department of Health. *The new NHS: Modern, Dependable.* Cm 3807 HMSO 1997

4.6.4 Technology appraisals guidance – the only one of NICE's guidance that carries a legal mandate on the commissioner to fund the intervention that the technology appraisal relates to. This covers new medicines. NICE have a recommendation to produce an assessment of a drug within 90 days of it receiving its product licence.

4.6.5 Interventional procedures guidance – only one of NICE's guidelines that take safety into account. However, since April 2009 the enforcement mechanism behind this has no longer been in place.

4.6.6 Previously Trusts were required to have a list of interventional procedures that NICE had considered, including details on requirements that NICE had put around these procedures. The Trust would oversee this and would keep a list of clinicians who wanted to take interventional procedures that NICE had not considered, and the Trust was responsible for referring these clinicians to NICE. The Healthcare Commission would check that the Trust had in place such mechanisms. However, this responsibility was not passed to CQC when CQC was formed from the merger of the Healthcare Commission, the Commission for Social Care Inspection and the Mental Health Act Commission in April 2009.

4.7. Key National Organisations for advising on pharmaceutical and medical device usage

4.7.1 The key national organisations concerned with cost, effectiveness and value for money of treatments are summarised in Figure H.12.

Dates	Organisation	Legal Status	Primary Purpose	Powers
07/1949 – 09/1971	Joint standing committee on proprietary preparations (**MacGregor Committee)**	Non-statutory, PropList was guidance. It was voluntary, but deviation from it could require special justification if a doctor was investigated	**NHS Cost saving** by recommending the prescribing cost-effective treatments	Could remove a product from the approved list of reimbursable products

1966	SubCommittee on Pregnancy Tests	SubCommittee of the Pathology Committee	**Set up to advise on the provision of pregnancy tests,** they looked at effectiveness, reliability, safety and cost to the NHS.	Advisory, made recommendations on what could be added to/taken from the relevant supply lists
1969-June 1998	Quality assurance system for manufacturers. It was run by the STB, the MDD, then the MDA	Voluntary quality assurance scheme for device manufacturers, known as the Manufacturers Registration Scheme from 1988 onward	**Manufacturer quality assurance system covering design and production.**	Advisory, it incorporated compliance inspections, but no hard powers. Ceased when the MDD came in as these functions were then statutory.
1969 - 2005	**It was run by the STB, the MDD, then the MDA.** Involved staff in 20 centres in hospitals and universities. In 2005 during this function was moved into the Centre for Evidence based purchasing within the NHS Purchasing and Supplies Agency.	Evaluation programme to inform the NHS about the safety and performance of equipment, including some medical devices.	**To provide independent advice for the NHS on the performance and function of equipment,** this did not include an assessment of cost-effectiveness.	Published reports and provided training to advise the NHS on safety and performance of equipment, including some medical devices. and assessed. Liaised with NICE to ensure complimentary rather than competing areas were researched.
1993-2002	**SERNIP**	Voluntary	**Classifying new treatments and procedures** to	Made recommendations on how new and

			recommend how they should be used in the NHS	innovative treatments should be used.
1999 -	**NICE**	Statutory agency, but guidance they issue is voluntary except for Technology appraisals	**Cost effectiveness** and **reducing variation** in the availability and quality of NHS treatments and care.	Produces guidance on which treatments ought be available; but only technology appraisals **have** to be made available by the NHS.

Figure H.12 Key National Organisations for advising on pharmaceutical and medical device usage.