The Independent
MEDICINES & MEDICAL DEVICES
Safety Review

The Independent Medicines and Medical Devices Safety Review

Written Evidence

This document contains information provided to the Independent Medicines and Medical Devices Safety Review in support of, or following, the Oral Hearings held between November 2018 and May 2019. You can find the previous submissions of those that provided them, as well as links to the Oral Hearings, on the Evidence page of the IMMDS Review website.

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

Leigh Day on behalf of OACS Charity, FACSaware, and Valproate Victims

Shared the following with the Review:

- International Notes Valproic Acid and Spina Bifida: A Preliminary Report – France. MMWR October 29, 1982 / 31(42);565-566 https://www.cdc.gov/mmwr/preview/mmwrhtml/00001180.htm

- Valproate: A New Cause of Birth Defects -- Report from Italy and Follow-Up from France. MMWR August 26, 1983 / 32(33);438-9 https://www.cdc.gov/mmwr/preview/mmwrhtml/00000129.htm

- Lindhout, D and Meinardi, H. Spina bifida and in-utero exposure to valproate. The Lancet. August 18 1984 p396

A Review of Evidence Submitted to the IMMDS Review on behalf of the Organisation for Anti-Convulsant Syndrome (OACS Charity), Valproate Victims and FACSaware[1]

Prepared in consultation with

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May 2019

[1] This document has also been prepared with the support of **OACS Ireland, APESAC (France) , ASSAC (Switzerland), ABVSV (Belgium)**, to whom our sincere gratitude is expressed.

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Opening Remarks

In the text that follows, we have attempted to provide a consolidated review of the evidence submitted to the IMMDS Review, over the last 12 months, in relation to Sodium Valproate.

This closing submission is intended to complement the initial submission made on behalf of OACS Charity, FACSaware and Valproate Victims ("Justice for FACS Kids") on 20 April 2018. That initial submission explored the justifications for redress for those injured by Sodium Valproate: We highlighted the 'double disability' suffered by those mothers who depended upon Sodium Valproate for seizure control during pregnancy and whose children were injured in utero. Fundamentally, we sought to spotlight the impact of FVS on the lives of many families across the UK who continue to live without redress and without compensation.

Over the last 12 months, the Review Panel has taken the opportunity to meet with many families to enable them to tell their own stories: We know that many of those who have been involved with this process have felt that they have been properly heard.

Now, as the IMMDS Review moves into its final phase, it is essential that there is renewed focus upon ensuring that the final recommendations made by the Review Team respond to the needs of those families, and to the questions identified by the then Secretary of State in setting up this process, in particular:

- *'Firstly, the robustness and speed of the processes followed by the relevant authorities and clinical bodies to ensure that appropriate processes were followed when safety concerns were raised;*
- *Secondly, whether the regulators and NHS bodies did enough to engage with those affected to ensure their concerns were escalated and acted upon;*
- *Thirdly, whether there has been sufficient co-ordination between relevant bodies and the groups raising concerns; and*
- *Fourthly, whether we need an independent system to decide what further action may be required either in these cases or in the future'*.

Mr. Hunt explained; *'**This is because one of the judgments to be made is whether, when there has been widespread harm, there needs to be a fuller, or even statutory, public inquiry. Baroness Cumberlege will make recommendations on the right process to make sure that justice is done and to maintain public confidence that such decisions have been taken fairly'**.*

As such, at the inception of the IMMDS Review, Mr Hunt, and his government, expressed a desire to ensure that 'justice is done'. In making their recommendations, the IMMDS Review Team have a once in a generation opportunity to secure 'justice' for those affected by FVS.

With the issue of 'justice', in the context of FVS very much in mind, this review of the evidence evaluates the formal testimonies provided to the Review by a range of professional stakeholders with whom the IMMDS Team have engaged; including clinicians, regulators, the manufacturer and experts.

The purpose of our evaluation is to ensure that the individuals and parents whose lives have been affected by Sodium Valproate and FVS, remain at the heart of the Review Team's final recommendations.

As explained in this further submission, we maintain that the evidence which has been provided to the Review Team, both on paper and in oral evidence, over the course of the last year, fundamentally supports the conclusion that:

- **The teratogenic risks of Sodium Valproate could and should have been recognised significantly earlier than they were;**

- **That had those risks been recognised earlier, different warnings could have been given by better informed clinicians to a very large number of women;**

- **Had appropriate warnings been provided earlier many women may well have made different treatment decisions in consultation with better informed clinicians.**

Any recommendations made by the Review Team must flow from that conclusion and seek to meet the needs of the individuals living with FVS in particular.

We maintain that those needs could be met by a recommendation for a no-fault scheme of compensation for those affected by FVSD. Such a scheme would avoid having to make the invidious individual causation decisions that compensate some but not all of those affected; the corollary is that with such a recommendation, the basis of compensation can be bespoke in form.

In our original submission we suggested, and now reiterate, the immediate need to:

- **Identify all of those who have been diagnosed as suffering from FVSD and who are receiving state benefits, Local Authority social care support and/or Special Educational support in primary, secondary or tertiary education; and**

- **Ring-fence existing benefits, social care and special educational provision and ensure that any other financial redress paid allows that ring-fenced provision to be maintained indefinitely; and**

- **Provide funding for and access to specialist NHS services at Regional Centres where the particular needs of children and young people affected by FVSD are recognised and can be met; and**

- **Provide for future care needs and reimburse the cost of care provision expended by families to date.**

We believe that the evidence from the Thalidomide Trust to the IMMDS Team reinforces the case made in our April 2018 submission, that the most successful mechanism of assessing and res-assessing needs and distributing periodically paid funds, is an independent trust rather than a part of the Department of Health. We are strengthened in that belief by the evidence emerging in the Contaminated Blood Inquiry: It is clear to us that any Trust instituted needs to be simple in structure and straightforward in the scheme that it sets out for its Trustees – the evidence from the vCJD Trust points to the way in which the best of intentions can be undermined by over-zealous drafting.

We are preparing a further paper setting out the mechanism and resources that we think will be necessary to equip such a Trust to deal with the process of meeting the historic, current and future care needs of the cohort of children/adults affected by FVSD.

Structure of this Submission

This submission reviews the evidence given to IMMDS from the key participating bodies: It aims to compare that evidence, and in particular the chronologies advanced through that evidence. There are differences in emphasis between participating bodies, and differences in the approaches that they have adopted: Plainly other evidence might well have emerged had this Review been equipped with the powers of a Public Inquiry. Nevertheless the evidence volunteered (allied to the answers elicited in oral evidence) provides a good broad understanding of the recognition of Valproate's effects. In that context we have identified a number of issues upon which the contrasting evidence submitted by participants highlights a range of concerns that have still not been addressed through the IMMDS Review process.

Whilst this Review is not formally concerned with issues of liability we have drawn attention to the fact that the risks posed by Sodium Valproate were, in our evidence, inadequately communicated to clinicians and patients for too long. We maintain that women prescribed with Sodium Valproate might have been differently warned, having regard not only to changing legal duties (with reference to *Montgomery*), but also acknowledging that irrespective of shifts in the legal landscape there are longstanding legal, moral and ethical obligations owed by regulators and manufacturers to equip Learned Intermediaries with accurate information to enable them to administer drugs safely and treat patients appropriately.

We have been mindful in doing this of the concerns of our clients, perhaps most pithily expressed in the FACSaware document sent to the Epilepsy APPG in December 2017:

- *" It has been proved beyond doubt and accepted by the pharmaceutical industry that there is an increased prevalence of physical and neurodevelopmental birth defects when Valproate is taken during pregnancy*
- *Those exposed have lifelong disabilities and have been unable to access justice in the UK Courts*
- *The services required by those affected and their families are highly specialized*
- *The taxpayer is paying for the services required and the pharmaceutical industry is not contributing*
- *Our Regulatory system is broken and needs to be fixed*

<u>Our Wish List</u>

- *Immediate additional funding for local education, health and care services*
- *Immediate and lifelong financial security for those exposed to Valproate who present symptoms of Valproate Syndrome*
- *Appropriate services delivered and coordinated by professionals who have an understanding of Valproate Syndrome*
- *A judge –led Public Inquiry into medicines and devices regulation to focus on Valproate "*

A. Introduction

On 10 October 2014, the European Medicines Agency's Pharmacovigilance and Risk Assessment Committee ('PRAC') recommended strengthening restrictions on the use of Sodium Valproate in women and girls as follows:

"Valproate should not be used to treat epilepsy or bipolar disorder in girls and in women who are pregnant or who can become pregnant unless other treatments are ineffective or not tolerated. Women for whom valproate is the only option after trying other treatments, should

use effective contraception and treatment should be started and supervised by a doctor experienced in treating these conditions.

Women who have been prescribed valproate should not stop taking their medicine without first consulting their doctor.

In countries where valproate medicines are authorised for the prevention of migraine, women must not use valproate for preventing migraine when they are pregnant. Pregnancy should be excluded before starting treatment for migraine, and women should use effective contraception.

The PRAC also recommended that doctors who prescribe valproate provide women with full information to ensure understanding of the risks and to support their decisions.

These recommendations follow a review of available data on the effects of valproate exposure during pregnancy. During the review the PRAC also consulted representatives of patients and families who have been affected as well as a group of experts and specialists. While valproate remains an option for patients where other treatments have failed or are not tolerated, the Committee concluded that women and healthcare professionals need to be better informed about the risks of valproate exposure in the womb and of the need for effective contraception.

Recent studies have shown a risk of developmental problems of up to 30 to 40% in pre-school children exposed to valproate in the womb, including delayed walking and talking, memory problems, difficulty with speech and language and lower intellectual ability.

In addition, data show that children exposed to valproate in the womb are at an approximately 11% risk of malformations at birth (such as neural tube defects and cleft palate) compared to a 2 to 3% risk for children in the general population. Available data also show that children exposed to valproate in the womb are at increased risk of autistic spectrum disorder (around 3 times higher than in the general population) and childhood autism (5 times higher than in the general population). There are also limited data suggesting that children exposed to valproate in the womb may be more likely to develop symptoms of attention deficit hyperactivity disorder (ADHD). "[2]

Comment

As evidenced by the extract above, from 2004, onwards there has been a recognition by national and international Regulators that Sodium Valproate is implicated in the causation of neural tube defects, malformations and neuro developmental effects. Co-ordinated prospective studies established at the beginning of the century have gradually revealed the full extent of these effects. This decision by the PRAC recognised the need to ensure that Valproate should not be prescribed for seizure control or for migraine in women of childbearing age. A consensus acknowledged by Sanofi for the first time in their subsequent amendment of SmPC's and PIL's to reflect this consensus, which were approved by MHRA in February 2015.

The review below looks at the history of the emergent risks associated with Epilim/Sodium Valproate since its first licensing, from the perspectives of

- Clinicians
- Sanofi ('The Manufacturer')

[2] Sanofi Submission to IMMDS: Response to Q 9 p 42

- CSM/MHRA ('The Regulator')
- Researchers

It is implicit in our review that it was at all times in the patients' best interests to be adequately warned of risks in consenting to long term treatment.

At the end of the review of evidence we put forward some ideas about the nature of consent to treatment as it applies to long term prescribing of drugs with an emergent risk profile (Section 11).

We also comment briefly on some further evidence that seems to us to be desirable for the Review to consider before making its final recommendations (Section 12).

B. The positions of the different parties revealed by the evidence

1. Association of British Neurologists

We note, within the evidence provided to the Review, the letter to Dr June Raine, Director, Vigilance & Risk Management of Medicines, MHRA from President and President-Elect of ABN: **28 October 2014** in relation to advice proposed by MHRA:

"It is being recommended that valproate medicines should not be used to treat epilepsy and bipolar disorder in girls, women who can become pregnant or pregnant women unless other treatments are ineffective or not tolerated."

Whilst we welcome further consideration of the risks and benefits of prescribing valproate in women with neurological conditions, we are requesting that this advice is urgently reconsidered and changed with respect to epilepsy, and especially in relation to the idiopathic (genetic) generalized epilepsies (IGE), which affect about 25% of all people with epilepsy. Epilepsy is a serious condition especially when associated with convulsive seizures, often starting in childhood and adolescence, a vital stage in educational and social development, and for some the time when they are first seeking employment. Only a minority will be considering, or be at risk of, pregnancy in the short to medium term, hence our concern about the proposal to withhold an effective treatment. If followed, this advice from EMA/MHRA will expose a significant proportion of girls and women to a period of uncontrolled seizures and associated injury, risk of sudden death (0.5% per year for people with uncontrolled seizures), educational compromise, and social disadvantage….

…Treating epilepsy is a balance of risk versus benefit, and there are not infrequent situations where the benefits of valproate outweigh the risks. Furthermore, current guidelines highlight the principles of informed decision making and the rights of the patient in doing so. If followed, the MHRA guidance would deny female patients that right.

In summary, we would wish to see the guidance changed as follows to include the facts that:

I. For IGE, valproate remains a first line treatment choice
II. For other forms of epilepsy, valproate can be used when benefits outweigh risks.
III. At diagnosis, any treatment decision must involve a discussion of benefits and harms of treatment options including teratogenicity. "

In a letter to Dr Sarah Mee, Senior Medical Assessor at Vigilance and Risk Management of Medicines at MHRA from the Honorary Secretary of ABN: **9 December 2014** responding to proposed guidance:

- **“***The short deadline for the response is extremely unhelpful and inhibits proper consultation on a very important issue.*
- *· Neurologists are highly experienced in discussing the risks and benefits of various antiepileptic agents. Our experts therefore question whether the use of such forms is appropriate and acceptable to the clinical community, particularly where a one-sided risk is portrayed for valproate, potentially to the detriment of women with epilepsy. The material should therefore mention the risks of inadequately treated epilepsy.*
- *· There is great concern amongst epilepsy experts that the current wording will be interpreted to mean there is an obligation on the prescriber to try the patient on an alternative medication before valproate, even when it may be the best drug for the individual. The substitution of patient centred clinical decision making with a rigid prescribing pathway has the potential to lead to significant morbidity and mortality for some women for whom valproate may be the only drug that works.*
- *· The evidence that valproate is solely responsible for developmental delay remains incomplete and our experts feel that it is presented too strongly as an argument in favour of using alternative agents before valproate.* **“**

By **April 2016** Guidance being circulated by the President of ABN includes the comment:

“Sodium valproate is used mainly for prevention of epilepsy, but also sometimes for treating bipolar disorder and occasionally for migraine prevention. There is now strong evidence that sodium valproate is a potent teratogen, causing major malformations including spina bifida in up to 7% of pregnancies (Morrow et al., 2006), but even more alarming, causing neurodevelopmental delay in the exposed foetus (mean reduction in IQ of 9 points at aged 3 and 6 years) and an increased incidence of autistic spectrum disorder (Meador et al., 2013). Nevertheless, sodium valproate is a very effective antiepileptic medication, and is the proven best drug for controlling genetic (idiopathic) generalised epilepsies (Marson et al., 2007). It is therefore the first-choice antiepileptic drug for young men with generalised epilepsies but, owing to the known teratogenic risks, it is used in women only as a last resort. Thus, young women with generalised epilepsies routinely receive second best treatments for their epilepsy. Inevitably, some women, with appropriate discussion and shared decision making, do opt to take sodium valproate for their epilepsy, knowing that they must avoid pregnancy whilst continuing to take this medication.

The new guidance from the MHRA aims to ensure that all women taking sodium valproate are fully informed—and are repeatedly reminded—of the teratogenic risks. “

The **June 2018** Newsletter of the ABN advises that:

“As neurologists, we know that valproate is a serious teratogen but we appreciate that it is also an effective anti-epileptic drug, and for some women with epilepsy, valproate may be the only drug that controls seizures. Until there is an equally effective safer alternative for this group of women we need valproate to remain available ……The ABN recognises the need for a safe alternative to valproate to be developed and the need to lobby for research to be funded to enable this. “

We submit *that amongst the clinicians responsible for the care of women with epilepsy, there is an apparently irreconcilable conflict in relation to the use of Sodium Valproate, between neurologists who want to achieve the best seizure control that they can for their patients for as long as possible and those who pointed to the developing learning about the drug and its effects and the possibility of causing harm by its unthinking re-prescription in*

women of childbearing age. Professor Clayton-Smith in her oral evidence pointed to the suggestion by neurologists that her research 'would get a good drug banned'.

Comment

We are concerned that this attitude allied to a quasi-institutional scepticism about the emerging evidence of effect, may have delayed the reaching of a clinical consensus about the effects of the drug and unnecessarily prolonged the time taken to agree the terms of the MHRA guidance until 2016. Whilst such scepticism about the effects attributable to an excellent Anti Epilepsy Drug ("AED') is unsurprising, the delay in warning patients of emergent risks has had the effect of diminishing neurologists standing as effective and informed Learned Intermediaries from the standpoint of Manufacturers.

2. Royal College of Obstetricians and Gynaecologists

On **24 April 2018**, t**he** Medicines and Healthcare Products Regulatory Agency (MHRA) announced that valproate medicines – used to treat epilepsy and bipolar disorder – must no longer be prescribed to women of child bearing age unless she is on a pregnancy prevention programme (PPP).

In response to this announcement, the College issued the below statement and safety alert by email to all UK members:

The Medicines and Healthcare Products Regulatory Agency (MHRA) has today announced that valproate medicines – used to treat epilepsy and bipolar disorder – must no longer be prescribed to women of child bearing age unless she is on a pregnancy prevention programme (PPP).

The medication significantly increases the risk of birth defects and developmental disorders in children born to women who take it during pregnancy. Up to 4 in 10 babies are at risk of developmental disorders, and around 1 in 10 are at risk of birth defects.

Healthcare professionals who prescribe valproate must ensure the woman is enrolled in a PPP, which includes the completion of a signed risk acknowledgement form and seeing a specialist at least every year.

These new regulatory measures are being supported across the NHS with other authorities also making changes – such as new GP system computer alerts – to ensure changes in prescribing behaviour take place promptly. Women who are prescribed valproate are encouraged to contact their GP and arrange to have their treatment reviewed. Women should not stop taking valproate without medical advice.

In **June 2016**, the College published its clinical guideline (Green-top Guideline) on the management of epilepsy in pregnancy. This guidance recommends that exposure to sodium valproate and other anti- epileptic drugs should be minimised by changing the medication prior to conception, as recommended by an epilepsy specialist after a careful evaluation of the potential risks and benefits.

It is also notes that women should be advised to seek advice from their GP and/or specialist team before conception or as soon as they are aware that they are pregnant. For women with epilepsy, the lowest effective dose of the most appropriate anti-epileptic drug should be prescribed and they should be looked after by a specialist team throughout pregnancy

The guideline was highlighted to all members in a bespoke email, via the College's e-newsletter, our website and social media.

We include a link to the RCOG Guidance on Consent: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/clinical-governance-advice-6/: We believe this link demonstrates the dialogue which has been required for some years. We rehearse below at Section 11 of this review of evidence, our views on the particular characteristics of consent for long term use of an AED.

3. Medicines and Healthcare Products Regulatory Agency

The MHRA is the current Regulator for Medicines and Healthcare products (including Medical Devices) and is an Executive Agency of the Department of Health and Social Care.

A) Overview

In its written submission to the IMMDS Review, the MHRA has provided the following narrative.

In 1971, the original licence application for sodium valproate in the treatment of epilepsy was submitted to the Department of Health. This application was considered by the CSM and its sub-committees. Valproate was initially restricted to use in hospitals and other centres specialising in the treatment of epilepsy before it was approved for general prescription in 1974[3]. Animal data available at the time of authorisation indicated that sodium valproate was teratogenic and the first datasheet dated 1974 indicated that valproate should only be used to treat women of childbearing age in severe cases or in those resistant to other treatment.

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

Additional warnings have been updated and communicated on numerous occasions since then in response to new and emerging evidence over time and following extensive scientific reviews. In 1982 the CSM considered a paper on sodium valproate and teratogenicity and advised that there was a need for specific research into anti-epileptics and teratogenicity and that there should be an article issued in to healthcare professionals in the bulletin 'Current Problems in Pharmacovigilance' warning about valproate and birth defects. This was issued in 1983. In 1990 additional information on

[3] See Section 3(F) below in relation to the issue of 'Epilepsy Specialist Centres': We would urge the Review to look at how the history and documentation available regarding these Centres might inform our understanding of Sodium Valproate prescription in the UK.

birth defects, particularly neural tube defects, and recommendations on diagnostic screening were added to the product information. In 1993 an article on the risk of neural tube defects was published in 'Current Problems in Pharmacovigilance'. Patient information leaflets became a legal requirement for all medicines in 1999 and in 2001 warnings in the product information for valproate were expanded to reflect the available evidence on birth defects and to state that women should be informed of the risks and benefits of continuing treatment.

In 2003, following consideration by the CSM working group on paediatric medicines of studies looking at valproate and developmental delay, product information was updated to state that women of childbearing potential should not be started on valproate without specialist neurological advice. Warnings describing the available evidence from epidemiological studies on developmental delay were also added and an article published in Current Problems in Pharmacovigilance. "[4]

Comment

As in the Submission by Sanofi, the MHRA emphasises the clarity of the warning given to clinicians from the outset that:

- The drug was potentially teratogenic
- Women of childbearing age should be prescribed the drug only if their epilepsy was 'severe' or 'resistant to other treatments'
- 'Any benefits which may be expected from its use should be weighed against the hazard suggested by its findings'

Epilim was from the first a very effective AED. It seems that for many neurologists the issue of its teratogenic potential was always subordinate to its effectiveness in seizure control. The critical question to pose to the Regulator is whether over time it questioned, sufficiently sceptically, the evidence it was being given by Sanofi about the drug's developing risk profile and whether it was sufficiently rigorous in making its own independent assessment of the Yellow Card system of Adverse Incident Reporting.

In short, is there more that our Regulator (and others) could have done to learn more about the nature and incidence of the emergent risks associated with Epilim in the 1980's and 1990's?

B) Regulation Powers

The MHRA have provided the following summary of UK medicine regulation:

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

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

• the Medicines Act 1968;

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

[4] MHRA Submission to IMMDS : p16

• EU Regulations.

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

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

• Medical devices
In the UK, the regulation of medical devices and in vitro diagnostic medical devices is

governed by:

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

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

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

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

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

The changes to the legislation were largely introduced to:

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

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

These powers can be categorised as "investigatory" – powers enabling us to acquire information in relation to business activities or specific devices – or "enforcement" – reactive powers to compel compliance with the law and address risks to public health."[5]

For medicines, Ministers also get dispassionate counsel from the Commission on Human Medicines, an independent advisory committee made up of professional and lay representatives required before advising to declare conflicts of interest, professional and personal.

Commission on Human Medicines (CHM)

The Commission on Human Medicines was established in October 2005. Its functions are set out in regulation 10 of the Human Medicines Regulations 2012 (SI 2012/1916).

The functions of the Commission on Human Medicines are:

- *to advise the Health Ministers and the Licensing Authority (LA) on matters relating to human medicinal products including giving advice on the safety, quality and efficacy of human medicinal products where either the Commission thinks it appropriate or where it is asked to do so*
- *to consider those applications that lead to LA action as appropriate (eg where the LA has a statutory duty to refer or chooses to do so)*
- *to consider representations made (either in writing or at a hearing) by an applicant or by a licence or marketing authorisation holder in certain circumstances*
- *to promote the collection and investigation of information about adverse reactions to human medicines so advice can be given.*

The Commission is similarly involved in respect of medicinal products to which relevant EC legislation applies.

The CHM's activities include:

- *giving advice on applications for both national and European marketing authorisations and considers further representation against its provisional advice in respect of national applications, either in writing or in person by the company.*
- *Commissioners also frequently attend the European Committee on Human Medicinal Products (CHMP) meetings as part of the United Kingdom delegation.*
- *advising on the need for, and content of, risk management plans for new medicines.*
- *promoting the collection of reports of suspected adverse drug reactions from health professionals and patients through the 'Yellow Card Scheme'. Data from the Yellow Card Scheme is used for the detection of new safety issues and in the investigation of issues raised from other data sources.*
- *providing advice on the impact of new safety issues on the balance of risks and benefits of licensed medicines and advises on appropriate risk minimisation measures. These may include adding warnings to product information for health professional and patients, restricting the use of a product or, in exceptional circumstances, suspending use of a product and/or revoking the marketing authorisation. In the event of urgent safety issues, health professionals will be informed via a letter from the Chairman of the Commission. Less urgent issues are*

[5] MHRA Submission to IMMDS : pp113-4

communicated via a bulletin entitled 'Drug Safety Update', which is issued in conjunction with the MHRA.

- *advising the licensing authority on changes to legal status of marketing authorisations."*[6]

C) Method of Regulation

The MHRA has the powers, how does it exercise them?

"The key questions for the MHRA are:

o Do the advantages outweigh the disadvantages of taking the medicine?

o Does the medicine do the most good for the least harm for most people who will be taking it?

o Are the side effects acceptable?
A high level of side effects may be acceptable for a medicine used to treat a life-threatening illness, for example, but not in one used for a common minor ailment.

Ultimately, patients and their healthcare professionals have to weigh up the pros and cons of each medicine when deciding on the most appropriate treatment.

Monitoring the safety and quality of medicines

There are several ways in which the MHRA checks the safety and quality standards of medicines and ensures that they comply with European and UK law and regulations. Inspections, reporting systems, and intelligence about illegal activity all play key roles.

As well at its own inspection teams and proactive monitoring, the MHRA relies on manufacturers, healthcare professionals, and the public to report defects, side effects, and misleading information.

The MHRA monitors safety and quality standards by:
Regular inspections of good and safe practice, including:

- *Medicines manufacture and supply of Medicines*
- *Distribution and storage*
- *Clinical trials.*
- *Laboratories testing medicines*
- *Inspection of blood establishments.*
- *Annual routine sampling of marketed medicines at manufacturers' premises, wholesalers, and pharmacies.*
- *Publishing standards on ingredients and expected quality for medicines (British Pharmacopoeia).*
- *Ongoing reports from healthcare professionals, patients, and manufacturers, including:*
- *Potential side effects of prescription and over the counter medicines and herbal remedies (Yellow Card Scheme)*
- *Defective medicines*
- *Serious side effects involving blood and blood components (SABRE).*

[6] MHRA Submission to IMMDS: pp115-6

- *Reviews of important new evidence on products.*
- *Commissioning research into medicines safety*
- *Assessment of misleading or incorrect information, including:*
- *Adverts*
- *Product labelling*
- *Product information leaflets.*
- *Gathering intelligence about illegally manufactured imported and counterfeit medicines and medical devices.*
- *Managing the Clinical Practice Research Database (CPRD), information from which is used to detect healthcare trends and monitor the safety and risk benefit of market licensed medicines.*
- *Legally enforcing regulations and statutory obligations, including checking on products that are not licensed as medicines.*

When a medicine is suspected, or known to be unacceptably safe, the MHRA immediately works with manufacturers, wholesalers and healthcare professionals on the most appropriate and timely action to take.

Sometimes this means a product has to be recalled and taken out of the supply chain. By law, manufacturers must report to the MHRA any important defects in medicines. The action taken is determined by the scale of the threat posed to the public's health. The MHRA is committed to responding promptly and appropriately to concerns.

Reports prompt investigations, which can result in the issue of warnings and alerts. The MHRA also has the power to prosecute when regulations have been breached. The courts can impose fines or prison sentences when the law has been broken. And the Agency can withdraw unlicensed/ illegal products from the market.

Warnings (Alerts) can be issued about defective medicines and side effects associated with medicines and blood and blood products. These are sent out to healthcare professionals and organisations, and publicised widely in print and online, including on the MHRA website on GOV.UK.

While warnings about side effects are issued and changes to the prescribing indications or doses made for licensed medicines, few medicines are withdrawn from use. That is because most work well and are acceptably safe." [7]

D) Decision makers

"There are three main groups within the MHRA involved in regulatory decisions:

- *Staff – the Agency's professional staff make many decisions about the safety and performance of medicines and medical devices on a day-to-day basis, and about the*
- *quality of manufacturing and the distribution of medicines. An Executive Board of senior staff oversees the work of the Agency and takes ultimate responsibility for the decisions made.*
- *Advisory Committees – groups of independent experts and lay representatives who advise on whether medicines and devices work and are acceptably safe, based on an evaluation of all relevant evidence, including that from the MHRA. These groups include the Commission on Human Medicines, its Expert Advisory Groups, and the Devices Expert Advisory Committee.*

[7] MHRA Submission to IMMDS : pp119-20

- *The Agency Board – which is made up largely of external members, acts in a supervisory and advisory capacity and has a particular role in assuring the quality of decision-making.*

In law, decisions by the Agency are decisions of the Secretary of State for Health who is accountable to Parliament. Ministers also make decisions on matters of significant public concern from time to time, advised by the Agency or its expert committees.

Comment

There is no doubt that the MHRA has the powers to intervene when a drug is shown to be changing its risk profile and to change the terms of a Licence in a restrictive way. The history of Sodium Valproate in the last ten years demonstrates that interventional ability clearly.

Current consumer concerns focus on whether:

- The MHRA is too slow to respond to ***signals*** suggesting emergent risks of serious injury from drug treatment as opposed to ***medical standard proof of causation***; and
- That caution arises from a reactive attitude to monitoring which is slow to accumulate data and recognise trends at an 'early warning' stage; and/or
- That caution recognises the resources which manufacturers can bring to bear politically and in legal action against Regulators perceived to be over interventionist in setting restrictive terms for licencing or relicensing, established pharmaceutical products

The key to being able to use the available powers effectively is to have access to the best data about a product from whatever source and to treat the different sorts of reported data with due weight depending upon the study that it comes from whether from the Yellow Card scheme (both in its historic and (from 2005) more patient focused form, the kinds of prospective study envisaged by Nicolai, Vles and Aldenkamp[8], from a Registry review[9] or from a Cochrane Review[10]as well as paying attention to articles/outcomes from purely observational studies. At all times we assume that as Regulator it will have pursued a precautionary approach to even the most successful/efficacious products

E) Did the MHRA (or its predecessors) always regulate Sodium Valproate in a precautionary manner?

The additional material for Q 24 identifies the *occasions between 1965 and 1986 when the Committee on Safety of Medicines or its Adverse Reactions Sub Group referred to or*

[8] 'Neurodevelopmental delay in children exposed to antiepileptic drugs in utero – a critical review directed at structural study bias" J Neurol Sci 2008:271:1-14

[9] eg Morrow J, Russell A, Guthrie E, Parsons L, Robertson I, Waddell R et al: "Malformation risks of antiepileptic drugs in pregnancy: A prospective study from the UK Epilepsy and Pregnancy Register" Journal of Neurology,Neurosurgery and Psychiatry:2006;77(2):193-98

[10] eg Weston J, Bromley R, Jackson CF, Adab N, Clayton-Smith J, Greenhalgh J et al "Monotherapy treatment of epilepsy in pregnancy; congenital malformation outcomes in the child". The Cochrane database of systematic reviews. 2016;11:Cd010224

considered Sodium Valproate. In its regulatory history [11]*there are relevant entries as follows from the CSM Minutes:*

- *May 1972: "on the evidence before them the Sub Committee are unable to advise the grant of the product licences for these preparations for the purposes indicated in the application since the animal toxicology, including teratology, provided is inadequate and the data which has been presented gives ground for concern in view of the expected long term administration of the drug*
- *June 1972: "on the evidence before them the Sub Committee recommend the grant of a product licence for one year for the purposes indicated in the application provided that promotion is limited to hospitals and other centres specialising in the treatment of epilepsy and subject to all patients being monitored for therapeutic efficacy and safety"*
- *28 June 1973: "Anticonvulsant teratogenicity (CSM/73/65) "…the action proposed by ICI with regard to the modification of the datasheet on Mysoline to include a statement about the incidence of congenital abnormalities in infants born to epileptic mothers. They did not however think that that the evidence was as yet sufficiently conclusive to be advised as a general condition in association with the licensing of all anticonvulsant preparations"*
- *26 July 1973 : Anticonvulsant Teratogenicity (minute 9 of 73/6) The Committee was informed that the Sub Committee on Adverse Reactions had accepted the Main Committee's view that it would be best not to mention the possibility of congenital abnormality following the use of anticonvulsants in relevant package inserts. The Sub Committee had still felt, however , that there was a case for mention to be made in data sheets to ensure that doctors were aware of the hazard, in part because of the possibility of litigation.*[12]*Whilst the Committee was sympathetic to this view they thought in practice it would be extremely difficult to make certain that the statement was included in all the relevant data sheets for the wide range of products containing anticonvulsant substances…… As the matter had been mentioned in the Chairman's letter sent to all doctors in May 1973 the Committee felt that reasonable steps had already been taken to see that the profession was alerted to the hazard and that in the light of this the Sub Committee would not consider it necessary to press for further action."*
- *30 August 1973: " Anticonvulsant Teratogenicity (Minute 3.3 of 73/7) The Chairman reminded the Committee of the Sub Committee's recommendation that all anticonvulsants should have an associated warning regarding possible teratogenicity. The Committee's views regarding the difficulties this presented had been conveyed to the Sub Committee but they still felt the evidence sufficiently strong to call for some action on the matter. In due course the Sub Committee would be submitting for consideration a report on the results of their survey of congenital abnormalities which was now being conducted on their behalf. Comment on the teratogenicity of anticonvulsants would of course be included in their report.*

  Publication of the report would help draw attention to the hazards of anticonvulsant treatment. The Chairman said that he had, however, discussed the matter with Sir Richard Doll, who had thought some earlier publicity would be welcomed by his Sub Committee. He had therefore agreed to discuss the question of how this might best be achieved with Dr Cameron of the BMA with a view to ensuring that all doctors were alerted to the hazards, yet without creating undue alarm

[11] MHRA Submission to IMMDS : after p192 et seq.

[12] The settlement of the Thalidomide Litigation in January 1973 would then have been uppermost in Committee Members minds

- *28 March 1974: Approval of a licence for Sodium Valproate in 'severe or resistant cases in women of child bearing age' with the express proviso that "This compound has been shown to be teratogenic in animals. Any benefit which may be expected from its use should be weighed against the hazard suggested by these findings"*
- *22 August 1974 : " Before proceeding with the variation, officials had sought the views of the Minister of State (Health) in view of the concern regarding the availability of drugs which could harm the foetus. On the understanding 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 relation to preparations containing phenytoin and phenobarbitone a datasheet warning as follows was agreed*

  "There is some evidence that anticonvulsant 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"

- *10 October 1980 : " Sodium Valproate may produce metabolic upset by interference with propionic acid metabolism, causing secondary hyperammonaemia…Should these symptoms occur Sodium valproate should be discontinued"*
- *16 December 1982: " The Committee concurred with the SEAR recommendation that there was a need for specific research into the role of anticonvulsant therapy in epileptic mothers in increasing the risk of congenital malformation of the foetus"*
- ***January 1983** : 'Current Problems' :" The risk to a woman with epilepsy who is receiving an anticonvulsant or delivering a malformed child is thus about one in ten. Nevertheless withdrawal of anticonvulsants is not generally advisable because fetal hypoxia due to maternal fits is likely to be at least as damaging as the drugs themselves…..Valproate ,like other anticonvulsants is known to be teratogenic in animals and one report suggests that it may also be teratogenic in humans"*

There is then a significant hiatus before the next relevant step identified by MHRA. It would be surprising if there had been no material discussion by CSM about Valproate during this period and we wonder whether the MHRA have been asked for any other material from this period. **Whilst it would be understandable if there was a concern not to burden IMMDS with unnecessary additional material, this seems a long unexplained gap.**

One possibility that should be explored is whether any of the material papers have been filed at the National Archives in any of the following sets which have been closed with a surprisingly distant release date. **We should be grateful if the MHRA could be asked to identify these files and explain whether they have any detail about or bearing upon the licensing or relicensing of Sodium Valproate/Epilim or of any reporting of any Valproate associated adverse events:**

Reference No		Title	Year	Release date
BN116/255	ARVI/84/3	Agenda,Minutes Papers	03/02/84	01/01/2085
BN116/254	ARVI/83/3	Agenda,Minutes,Papers	28/10/83	01/01/2084
BN116/253	ARVI/83/2	Meeting 2	01/07/83	01/01/2084

Bn116/352	ARVI/85/2	Meeting 2 Agenda	07/06/85	01/01/2086
BN116/353	ARVI/85/3	Meeting 3	04/10/85	01/01/2086
BN116/256	ARVI/84/2	Meeting 2	01/06/84	01/01/2085
BN116/351	ARVI/85/1	Meeting 1	01/02/85	01/01/2086
BN116/252	ARVI/83/1	Meeting1 Agenda missing	04/03/83	01/01/2084

The references from 2002 and 2003 show the Working Group assessing evidence from Adab, Dean and Craig, papers which were later to be used as the basis for the issuing of guidelines by NICE in 2004:

- *27 November 2002: "the Working Group considered that there was now evidence from a number of studies suggesting an increased risk of developmental delay following in utero exposure to sodium valproate. The WG advised that product information should be updated to include a warning of this possible risk"*

- *September 2003 : 'Current Problems in Pharmacovigilance': "Following a review of the available data including data from the UK Pregnancy and Epilepsy Register, CSM has advised the following*

  Women of childbearing potential should not be started on sodium valproate without specialist neurological advice

  Women taking sodium valproate who are likely to become pregnant should receive specialist advice because of the potential teratogenic risk to the fetus

  If taken during pregnancy sodium valproate should be prescribed as monotherapy at the lowest effective dose, in divided doses and if possible as a prolonged release preparation

  Folate supplementation prior to pregnancy may reduce the incidence of neural tube defects in infants born to children at high risk. Women should take 5mg of folic acid as soon as contraception is discontinued"[13]

The set of meetings from 2013 onwards show the recognition of the need for an overhaul of the prescribing guidelines for Epilim in the light of the need to warn of the risks associated with the drug that research had by then established to a medical standard of proof:

[13] The three supporting papers are
Adab N et al J Nerol Neurosurg Psych 2001; Jan(1) 15-21
Dean JCS et al J Med Genet 2002 ; 39: 251-259
Craig et al Epilepsia 2002; 43: Suppl 8 079

- *2 October 2013: neurodevelopmental effects including Autistic Spectrum Disorder*
- *26 February 2014: Further information about Autistic Spectrum Disorder(ASD) Childhood Autism and Intellectual disability measured by IQ testing*
- *18 June 2014: Issues considered : Links between Sodium Valproate and ADHD; Effects of Sodium Valproate on motor development; Dose dependent adverse effects; Effects of folic acid on teratogenicity ; Sodium valproate and breastfeeding ; Benefit/risk of sodium valproate in different indications – Epilepsy, Bipolar disorder and Migraine; Women of child bearing potential who are not pregnant; Women of child bearing potential who are pregnant; Infants exposed to sodium valproate in utero ; Proposed Regulatory actions*
- *11December 2014: Consenting patients for treatment with Sodium Valproate*
- *2 August 2017: pregnancy Prevention Programme*
- *31 October 2017: the need for a contraindication for the prescription of sodium valproate in epileptic women of childbearing potential not using contraception. The detailed conclusions of the meeting set out the strategy for removing Sodium Valproate as a first line AED for women of childbearing age with epilepsy*

1) Valproate should be contraindicated in pregnancy and women of childbearing potential not using effective contraception

2) This should be supported by a bespoke 'Pregnancy Prevention Programme' for women of child-bearing potential who need valproate treatment with the requirement for pregnancy testing dependent on the method of contraception used, applicable to all indications and also in any off-label use

3) A signed 'acknowledgement' or 'consent' form should be routinely used when women are reviewed on an annual basis by a specialist in the context of shared care arrangements

4) A registry should be set up to record and track women taking valproate and monitor compliance with the Pregnancy Prevention Plan and any exposed pregnancies

5) Changes to GP prescribing systems to introduce alerts and information on the pregnancy prevention programme should be implemented to support these measures

6) Smaller pack sizes which support individual pack dispensing should be made available to ensure that warnings about use of valproate in pregnancy reach women

7) A pictogram, supported by appropriate user testing, should be introduced on valproate labelling as endorsed by patient organisations

The MHRA was asked promptly to take forward the following actions to be considered at the next meeting:

1) Prepare a summary of distribution metrics of the valproate toolkit, measures taken to ensure compliance with the regulatory position to date and an analysis of the reasons for the lack of impact

2) Prepare a detailed proposal for a bespoke valproate Pregnancy Prevention Programme including a patient registry

3) Work with GP software system providers to upgrade alerts for valproate on GP systems such that these support appropriate prescribing, regular annual review of women of child-bearing potential and the implementation of a bespoke valproate Pregnancy Prevention Programme.

4) Further progress the implementation of shared care arrangements for women of childbearing potential who need treatment with valproate

5) Prepare a strategy for communication of the new regulatory position together with key stakeholders.

The group concluded by emphasising the urgency of making progress with regulatory actions in light of (a) the available data on the extent of ongoing use of valproate in women of child-bearing potential; and (b) the survey evidence of the proportion of women who have not received information on the risks in pregnancy or advice on contraception. "

Comment

It is clear from the outset, before ever Sodium Valproate was licensed that there was serious concern about its teratogenic potential. Sir Richard Doll as Chair of the Adverse Reactions Sub Committee of the CSM was insistent on conveying these warnings to practitioners in August 1973 via the BMA despite resistance from CSM.

Such concern was only allayed by establishing that it was no worse in this respect than the established anti-epileptic drug, Phenytoin. It is implicit in the CSM Minutes that another effective AED would be highly desirable at that time, also that the word 'teratogenic' had a particular resonance for epidemiologists of that Thalidomide era.

In this context, it is perhaps surprising that the risk warning required for Sodium Valproate in 1974 was less restrictive than that required for other anti convulsants containing phenytoin and phenobarbitone.

The concern about malformations identified in 1982 and publicised in January 1983's "Current Problems" appears not to have been followed up (or at least there is no evidence of follow up in the MHRA Submission). Nor is there any evidence of close interest in the continuing saga of reported malformations and emerging evidence of neuro developmental issues during the 1980's and 1990s. The CSM next examines Sodium Valproate in November 2002, roughly twenty years after first expressing concern about malformations.

Either there is missing information from MHRA – perfectly possible in any large organisation – or this is symptomatic of the lightest of light touch regulation and perhaps an institutional lack of curiosity: That seems extraordinary given the number

of women patients being prescribed the drug at this time and the number of publications on the relationship of Sodium Valproate with teratogenic effects.

By November 2002 it can be seen that the CSM has reacted to three studies about teratogenic risks whose conclusions are alarming and it begins to take steps to publicise these findings in a serious way. These steps lead to guidelines being drawn up by NICE and a campaign of publicity which can be said to bring warning of risk into far sharper focus by 2004.

The work from 2013-18 , when the long term prospective studies have reported, is as expected an exemplary exercise of pharmaceutical regulation to protect the position of women with epilepsy of childbearing potential.

But the period from January 1983 to November 2002 needs further explanation.

F) What was the Role, Purpose and Function of Epilepsy Specialist Centres Est.1972

In the oral evidence provided by Ms Moore on behalf of the MHRA, reference is made to the National Hospital - Chalfont Special Centre established in 1972, in the wake of the Reid report into people with epilepsy.

Aside from Ms Moore's veiled allusion to the Centres, the evidence provided to the Review to date has done nothing to interrogate the nature of the work done at these specialist centres, particularly regarding the extent to which the centres were used to establish the safety of Sodium Valproate for adult patients, minors and for babies in utero.

Our own research has identified Hansard reports which provide further information about these centres[14], however, given the parallel chronology of the institution of these epilepsy Centres and the introduction and development of Sodium Valproate in the UK, we would urge the Review to use its investigatory powers to request further information of the MHRA and other relevant bodies in relation to these centres.

4. Manufacturers – Sanofi

Sanofi is the leading European manufacturer of Sodium Valproate and was such during the period from 1981 onwards. Its submission sets out a history of the development of its compound and its detailed narrative of the emergence of teratogenic effects in the children of women with epilepsy who took the drug during pregnancy.

A) Overview and setting of context.

"*OVERALL STATEMENT*

Valproate is an essential medicine as defined by the WHO:

- *It remains one of the most effective treatments in generalised epilepsy and, for some patients suffering from certain resistant epilepsies, it is the only treatment to provide adequate seizure control.*

[14] HoL debate: Care of epileptics: The Reid Review
CARE OF EPILEPTICS: THE REID REPORT: HL Deb 27 January 1972 vol 327 cc474-87474§6.17 p.m.

- *Valproate is an important treatment that thousands of men and women in the UK continue to rely on to control seizures during their lifetime. The health risks from poor control of seizures should not be underestimated.*
- *During the most recent Article 31 EU referral, which concluded this year, the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) consulted widely and extensively in relation to use of valproate, and concluded that the benefit-risk balance of the product remains favourable, taking into account the agreed amendments to the product information and other risk minimisation measures.*

Sanofi has, at all material times, communicated the risk associated with valproate, as approved by regulatory authorities, consistent with the medical and scientific knowledge available at the time:

 The scientific evidence in relation to the risks of valproate and other anti-epileptic drugs, when used during pregnancy has taken many years to evolve, as a consequence of the substantial ethical difficulties associated with clinical research in pregnant women and the multiple confounding factors which may affect outcomes (including different epilepsy syndromes and seizures, other medical conditions and medicines and environmental factors). These difficulties are magnified in the context of any investigation of developmental delay or autism spectrum disorders where problems may not be identified until some time after the birth of the affected child and the role of events and exposures during early childhood is uncertain.

- *Processes for the reporting of adverse effects associated with use of medicinal products have been in place at all times while valproate-containing products have been supplied in the UK. Sanofi has fully complied with these processes as they have developed over time.*
- *Sanofi has ensured - and continues to ensure - that reports of adverse effects, emerging safety concerns and scientific data are promptly reported to the regulatory authorities, consistent with pharmacovigilance obligations so that the benefit risk profile of valproate products may be kept under constant review in the context of product information and other risk minimisation measures.*
- *As knowledge regarding valproate has developed, Sanofi has regularly reviewed and updated the product information (especially the SmPCs and the PILs), as approved by the regulatory authorities, so that HCPS and patients receive information on usage based on contemporaneous scientific and medical evidence.*

Sanofi works under the supervision of the regulators so that the risks associated with valproate use during pregnancy are appropriately communicated to patients, doctors and pharmacists:

• Sanofi participated in the Public Hearing held by the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee, in September 2017, as part of a review of the safety of valproate-containing medicines in women and girls who are pregnant or of childbearing potential. At this hearing, Sanofi suggested a number of measures to support risk minimisation, including the introduction of a pregnancy prevention programme and the use of regular (at least annual) treatment reviews.

 In 2018, Sanofi worked with the Medicines and Healthcare Products Regulatory Agency (MHRA) to implement the measures recommended by the PRAC following its review and promptly to produce and distribute over 150,000 copies of the new risk minimisation materials, to all HCPs, including GPs, neurologists, epilepsy nurses and

pharmacists, to ensure HCPs and patients are aware of the new contraindications to the use of valproate in pregnant women with epilepsy, unless specific conditions are met and requirements for a pregnancy prevention programme in women of child bearing potential.

 Sanofi has also participated in various initiatives to increase knowledge, understanding and awareness among HCPs and patients, beyond updates to SmPCs and PILs, both now and in the past. Notably, Sanofi has provided financial support to research and increased access to all relevant new information, consistent with the approved SmPC. By way of example, in 2017 Sanofi developed a tool for the NHS IT dispensing systems that uses a pop-up alert for pharmacists considering dispensing valproate for women of childbearing potential. Sanofi is pleased that the pop-up alert system Sanofi has developed has been taken up by NHS Digital to include on GP prescribing systems. Sanofi is currently producing separate HCP and patient-facing websites, and taking part in conferences and seminars to help explain the new risk minimisation requirements to HCPs.

Historic context is needed:

While we understand the Review wishes to assess the historic evidence relating to the regulatory approval of valproate medicinal products and the decision making and actions taken based on the medical and scientific knowledge at various times, we ask that the evidence is examined in the context of the contemporaneous regulatory requirements, the available alternative treatments throughout the time, the approaches to communication of information to patients which were regarded as appropriate at various times and the cultural norms of that time.

It would not be fair or true to the evidence and facts of the situation of the time for the review to seek to make recommendations based on current views and standards and with the benefit of hindsight of what 'should' have happened: Terms of Reference 'Scope of the Review' and section 'B Sodium Valproate', paragraph ii. "

Comment

There are caveats to be expressed in relation to a number of the points made in this Overall Statement, specifically

1. ….'*communicated the risk associated with valproate, as approved by regulatory authorities, consistent with the medical and scientific knowledge available at the time'*.

   We believe that there is good evidence to suggest that evidence of serious risk of malformations and neurodevelopmental delay associated with valproate went uncommunicated both to clinicians and patients during the 1980's and 1990's when a precautionary approach to consenting patients was mandated by good clinical practice even before the wider warning obligations imposed by the **Montgomery** judgement.

2. ….'*The scientific evidence in relation to the risk associated with valproate and other epileptic drugs when used during pregnancy has taken many years to evolve as a consequence of the substantial ethical difficulties associated with clinical research in pregnant women and of the multiple confounding factors which may affect outcomes'.*

We suggest that those ethical difficulties could have been surmounted far earlier than they have been, with the adoption of better ascertainment of Adverse Incidents and the earlier commissioning of case control studies of appropriate power to influence the views of Regulators.

Even in the 1980's before widespread computerisation of large scale studies, case control research revealed numbers of significant pharmaceutical adverse effects; a Registry for Valproate alone or all AED's would surely have been feasible earlier than 1996.

There seems to be little evidence of the Regulator requiring manufacturers to commission research to explore the extent of malformation effects revealed in independent studies. Particularly in a drug first licensed with an admitted teratogenic potential

3. *'These difficulties are magnified in the context of any developmental delay or ASD where problems may not be identified until sometime after the birth of the affected child'*

This mitigation would be more impressive were there evidence of earlier response to the emergent evidence of neurodevelopmental delay. In the UK, the initiative was left with independent researchers at Manchester University until 1999 to undertake a prospective study funded/commissioned by the National Lottery rather than by either manufacturer or regulator.

4. *"Sanofi has ensured – and continues to ensure – that reports of adverse effects, emerging safety concerns and scientific data are reported promptly to the regulatory authorities, consistent with pharmacovigilance obligations so that the benefit/risk profile of valproate products may be kept under constant review in the context of product information and other risk minimisation measures"*

We would typify Sanofi's approach as passive and lacking a sufficiently precautionary element in the light of the very serious adverse events associated with this drug which were emerging from 1979 onwards and for much the period from licensing until the late 1990's.

We particularly note the evidence of hepatotoxicity in children leading to a number of deaths as early as 1979, the early evidence of spina bifida reported in France in 1982 (and the 'Dear Doctor' letter written to US clinicians in that year) as well as the evidence of neuro developmental delay first reported in 1989-90***.*** ***See Appendix A***

5. *"Sanofi has regularly reviewed and updated the product information (especially the SmPC's and the PIL's) as approved by the regulatory authorities, so that HCP's and patients receive information on usage based on contemporaneous scientific and medical evidence'*

Whilst we accept that since –arguably- 2004, but more likely 2008, there is now a real time relationship between emerging information about risks and effects of Epilim and the giving of warnings directly to patients and clinicians.

The position prior to 2004, so far as patients were concerned, amounted to being told to 'ask your GP'. This was unsatisfactory in itself but when allied to the

significant lag between warning signals from Adverse Incident Reporting and the expression of accurate warnings of risk to clinicians in SmPC's, this created an environment in which clinicians consenting patients for treatment with Epilim were not able to paint an accurate picture of the true risks of a pregnancy involving treatment with Epilim.

Whether that was because of the strictures on warnings imposed by the Regulator or because of representations made to the Regulator by Sanofi, it is difficult and unnecessary to judge. What can be said is that for a significant period prior to 2004 treatment with Epilim for women of childbearing age was uncertain in risk assessment and probably ran risks that would have been avoidable had their treatment during pregnancy been with other AED's.

6. *"Sanofi works under the supervision of regulators…"*

In the examples given of recent exemplary practice, the improvement in risk assessment and warning must be acknowledged and welcomed as a significant improvement on the position prior to 2004.

7. *'Historic context is needed'*

Sanofi asks that '*the evidence is examined in the context of the contemporaneous regulatory requirements, the available alternative treatments throughout the time, the approaches to communication of information that were regarded as appropriate at various times and the cultural norms of that time'.*

That involves a number of different judgments to be made by this Review:

- Whether there really was candour in the relationship between Sanofi and its Regulator, or whether there was only, from Sanofi's side, a culture of bare compliance with Regulatory obligations notwithstanding its wider knowledge of the pharmacology of the product prior to licensing and thus its wider contextual understanding of the reported Adverse Incidents?
- Whether the attitude of both Sanofi and its Regulator towards accumulation of Adverse Incident Report data and the commissioning of responding research, during the 1980's and 1990's was sufficiently rigorous, having regard to Epilim's known teratogenic potential?
- Rather than simply gathering AIR's should a UK Registry for Epilim have been established as soon as concerns about neural tube defects emerged in the early 1980's?
- Why was there no UK equivalent of the 'Dear Doctor' letter sent out in 1982 in the United States, which was based on the findings of the Rhone Alpes study? What steps can Sanofi and the Regulator point to as evidence that this early study was being taken seriously?
- If appropriate research was being undertaken by Sanofi and a precautionary approach was being adopted by both Sanofi and the Regulator why did it take more than 20 years from the birth of the first Epilim-associated spina bifida baby for a warning to patients to appear in the PIL's?
- Whether in the early 1990's there was a point at which the Regulator should have recognised that whilst there was evidence of injury arising from all or most Anti Epileptic Drugs, the evidence of injury caused by Epilim was significantly greater and should thus have acted sooner to publicise that effect to clinicians?

- Communication of risk to patients is governed by the decision in ***Montgomery v Lanarkshire Health Board***[15] which reflects changing expectations in the explanation of risk/benefit in medical treatments to patients. That decision would govern any judicial assessment of warnings given to patients throughout the period during which Epilim has been licensed.

B) Response to Question 9

Sanofi's timeline exposition of Epilim from 1967 to 2018 occupies 59 pages of its submission to the Review in a detailed rehearsal of the material history from discovery of the anti-epileptic qualities of the drug in 1967 through to the steps taken with MHRA and EMA in 2018 to acknowledge and legislate for the effects of the drug on the children on some of those women who took the drug during pregnancy.

Much of this history is uncontentious if read with the caveats expressed above but there are certain points in the narrative where further comment is necessary.

1981

When Sanofi took over the Labaz group and acquired its product range which included Epilim was it aware of the concerns about hepatotoxicity (and at least one death in the UK[16]) apparently caused by paediatric prescription?[17] Assuming that it was did it share concerns with the Regulator?

The data sheets (SmPC's) at that time included these contraindications

> *'In women of childbearing age, Epilim should be used only in in severe cases or in those resistant to other treatment"*

and

> '*Women of child bearing age: Valproic acid or sodium valproate, like certain other anti-convulsants, have been shown to be teratogenic in animals. In women of child bearing age, the benefits of these compounds should be weighed against the possible hazard suggested by these findings'*

This text suggests a selective or even a restricted usage to those women with a 'severe' presentation of epilepsy. Is there any evidence of the proportion of women with epilepsy who were treated with Sodium Valproate over the following years apart from that volunteered by Sanofi in response to Question 4 which shows market share diminishing from 12.1% to 9.1% between 2013 and 2018.

Within those percentages, the number of women of childbearing age receiving Sodium Valproate has reduced from 17,172 to 15,633. Those of childbearing age using Depakote has reduced from 8,177 to 5,002.

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[15] (2015) UKSC 11

[16] See eg Hansard: HC Deb 27 November 1979(Vol 974;1253-64):HC Deb 22 May 1981 (Vol5;218W): HC Deb 27 July 1981 (Vol 9;345W): HC Deb 28 July 1981 (Vol 9;433W);HC Deb 27 April 1982 (Vol 22;236W):

[17] See eg "Acute hepatic failure associated with the use of Sodium Valproate " Suchy FJ et al N Engl J Med (1979) 300 (17) 962-6

Is it possible to trace the pattern of usage of this dug in prescriptions by neurologists and GP's over the period of its licence from 1974 onwards, to estimate whether or not it has been consistently prescribed only for 'severe' epilepsy?

October 1982: The Rhone Alps study[18].

'The flaws in the study were noted by various commentators…'

Equally, this paper was treated as a starting point by many independent researchers because it established that Sodium Valproate could severely damage a neural tube in a developing fetus. It also raised the question of what other damage the drug might do if taken during pregnancy.

The US Food and Drug Administration wrote to each US clinician about this report and required packs of drugs to contain a warning of risk based on its findings.[19]

A letter to 'The Lancet' followed on 13 November 1982[20]

Sanofi's comment that:

'The DHSS indicated … that they did not believe the data available at that time were sufficient to establish a causal connection between use of sodium valproate and neural tube defects or that any change to the datasheet for Epilim was necessary.'

This is surprising in the light of the US FDA's 'Dear Doctor' letter and to suggest that it was prepared to wait for evidence to emerge rather than to seek actively to identify evidence that might bear out the teratogenic effect identified in Labaz's animal studies.

Whilst it would properly have sought advice from DHSS as to any proposed variation of warnings based on changing evidence, it would be surprising if the Regulator itself would have had access to a greater amount of information about the pharmacology of the drug than Sanofi itself upon which to base any view about causation.

At this point – and later – Sanofi appears to have been content to accept Regulatory guidance rather than be seen itself to initiate a precautionary approach to identifying emergent risks being run by the patients prescribed its drug.

1983

Epilim was not yet established as the market leading drug that it subsequently became and any firm evidence of serious risks associated with its prescription would have been understandably unwelcome on the part of the manufacturer, nevertheless such commercial considerations could not have been permitted to override obligations to accurately warn the Regulator, clinicians and patients about changes in the risks seemingly associated with Epilim.

[18] CDC.Valproic Acid and Spina Bifida: A Preliminary Report – France. MMWR 1982

[19] See Appendix A

[20] Bjerkdal T et al : Valproic Acid and Spina Bifida

Furthermore, we submit that it should have identified a strategy for the company to investigate or commission investigation of those emergent risks over the subsequent decade. In our view, it is not sufficient to conclude that:

'any well-designed study attempting to reproduce the results obtained by Dr Robert would be impracticable, in view of the large numbers of patients it would be necessary to recruit, the small numbers of pregnant women who were prescribed Epilim, given the restriction on use of the product in women of childbearing age and the associated warnings set out in the datasheet and the fact that any study would require participation by very substantial numbers of healthcare professionals.'[21]

Looking at the problem as it might have appeared in 1983 rather than with the benefit of hindsight, it is hard to think that any other person or organisation was in a better position than Sanofi to initiate such a study (despite these constraints), nor to be able to arrange the multi-national aspects that that study would in likelihood have required. Such a comprehensive study would also have directly benefited the patients taking Sanofi's drug.

The data derived from such a study would have reached a definitive view about causation of neural tube defects far earlier and such a study would also have enabled signals about malformations and neurodevelopmental delay to be registered earlier.

Whilst from January 1983 the Epilim datasheet advocated careful monitoring where the drug was prescribed to an epileptic mother, there seems to have been no effort to formalise the collation of the outcomes of such monitoring save through the conventional notification system, either by Regulator or Manufacturer.

'the overall conclusion of the epilepsy experts who attended was consistent with the CSM's Current Problems issued earlier in the year, that it was uncertain whether anti -epileptic medication, including sodium valproate, produced teratogenic effects in humans, in view of the possibility that the effects which had been described, could be attributed to other factors, including epilepsy itself' (our italics)

The Current Problems Sheet itself[22] *is more forthright*

"Sodium Valproate (Epilim) and Congenital Abnormalities

Almost all surveys show a two to three-fold increase in the incidence of congenital anomalies among babies born to epileptic women. The most frequently occurring defects, in 2285 children exposed to anticonvulsant therapy in utero were cleft lip with or without palate (3.0%), skeletal anomalies (1.9%), congenital heart disease (1.4%), Central nervous system CNS defects (1.2%), anomalies of the gastro-intestinal tract (1.1%), facial and ear abnormalities (1.0%), mental retardation (0.7%), genito-urinary anomalies (0.6%). Other isolated anomalies occurred. The risk to a woman with Epilepsy, who is receiving an anticonvulsant, of delivering a malformed child is thus about one in ten. Nevertheless, withdrawal of anticonvulsants is not generally advisable because fetal hypoxia due to maternal fits is likely to be at least as damaging as the drugs themselves.'

[21] Sanofi Submission to IMMDS: Question 9 p 4

[22] CSM: Current Problems Sheet No.9: January 1983

'The malformations reported to occur with Valproate are similar to those with other anticonvulsants, namely neural tube defects, congenital heart lesions, digital anomalies and oral clefts. The recent recommendations that 'newer' drugs such as Valproate may be the drugs of choice for treating epileptic women cannot be accepted uncritically. A new drug may only appear less hazardous because evidence of hazard has not accumulated."

This conclusion would surely have reinforced for both Regulator and Manufacturer to decide on appropriate action to take about the problem that a very successful drug might be the cause of teratogenic effects not in patients but in their children. Determining this issue was likely to take a significant sized study, serious financial resources and several years but what would have been lost in starting such a research study as soon as possible?

1984

The Rhone Alps paper was followed by a Dutch paper from Professor Lindhout and Dr Meinardi (who had spoken at the International Symposium in 1983), with similar findings[23].

The WHO Bulletin's comment that 'no Regulatory Authority has subsequently 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' is a contemporary comment made before

- there was a widespread acceptance of the causal relationship between Epilim and neural tube defects
- there had been many published studies identifying association between Epilim and malformations
- there had been any papers identifying association between Epilim and developmental delay at a time when many mothers with epilepsy would have considered repairable spina bifida as an acceptable risk had they been warned of it by their neurologists.

1986 -1989

The 1985 CRM Annual Report introduced proposals, endorsed by the Committee on Safety of Medicines for providing information to doctors prescribing medicines for use during pregnancy. This advice seems to have been adopted in the next Epilim datasheet iteration (1989-90) which states:

'Some studies have demonstrated an increase in the expected incidence of congenital abnormalities born to mothers with epilepsy both untreated and treated.

There is evidence of teratogenic effects with anticonvulsants including Epilim in animals and there have been reports of congenital abnormalities in offspring of a small number of epileptic patients receiving therapy during pregnancy.

[23] Lindhout D, Meinardi H: Spina Bifida and in utero exposure to valproate. Lancet 1984 ; ii:936

In pregnancy, the benefits of these compounds should be weighed against the possible hazard suggested by these findings and their pregnancies should be carefully monitored'.[24]

It is not clear what assistance any clinician would have derived from this guidance in consenting a patient for treatment with Epilim. Some degree of association is referred to between congenital abnormalities and anticonvulsants, implying that Epilim is no worse in effect than its competitor anti convulsants[25].

The need for 'careful monitoring' is not as a part of a comprehensive programme of follow up organised by Sanofi or required by the Regulator The absence of a follow up from the Rhone Alpes survey and/or the failure to create a specific Registry to which concerned clinicians could return results of local monitoring of patients or from whom regularly updated results could be sought, was by this time surprising, given the number of published articles about Epilim and its effects, the increasing numbers of patients with epilepsy being treated during pregnancy and the wider compass of reported effects in the literature[26].

At this stage, it seems likely that there was a consensus amongst neurologists that Epilim should be prescribed during pregnancy, particularly for Idiopathic Generalised Epilepsies (IGE). Warnings given would follow the datasheet information which beyond identifying the possibility of spina bifida gave little specific guidance about other effects or guidance on dosage.

As indicated above, as late as 2014, the Association of British Neurologists was emphasising to the Regulator that the advice from the European Medicines Agency and itself

'will expose a significant proportion of girls and women to a period of uncontrolled seizures and associated injury, risk of sudden death (0.5% per year for people with uncontrolled seizures), educational compromise, and social disadvantage'[27]

Pharmaceutical and Medical Device manufacturers have a legally complicated relationship with patients who are end users of their products. They produce products and attach safety warnings to their products which have been agreed as appropriate by the Regulator.

Pharmaceutical manufacturers produce direct warnings (Summaries of Product Characteristics ('SmPC's') to clinicians who assess that their patients may benefit from prescription of their drug as well as (from 1990 onwards) direct warnings to patients included in the packs in which the prescribed drugs are supplied (Product Information Leaflets ('PIL's').

Consent to treatment with this drug prior to 2016 when the Valproate Toolkit, (with its emphasis on prescription of Epilim only to those with otherwise intractable epilepsy and pregnancy prevention), was agreed, involved a dialogue between a neurologist and a patient which covered the risks and benefits of the drug perceived at that time.

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[24] Sanofi Submission to IMMDS: Question 2 p 10

[25] In oral evidence (26 November 2018), Professors Clayton-Smith and Turnpenny and Dr Bromley expressed the view that by 1990 or 1991, a distinction could have been drawn between the effects of Epilim and other anti convulsants; in particular the more serious effects of Epilim.

[26]

[27] Association of British Neurologists Submission to IMMDS: December 2018. Appendix 2

This consent, as in any long-term treatment, was conditional in operating to the point of the next Treatment Review, which might be eighteen months or two years away; whilst there would be re prescription in the meantime by the patient's GP, the treatment would operate under the terms of the consent from Initial Consultation to Review to Review.

The importance of the warnings agreed between Sanofi and the Regulator was that this information was the basis upon which a reasonably competent clinician might rely without liability in warning a patient of risks involved in taking the drug, whatever the wider concern and ferment arising from the debate amongst researchers about the scope of effects not being warned about.

An extremely helpful summary of the evolution of warnings is amongst the evidence submitted to IMMDS.[28]

The complaint made by patients is that the warnings given, from licensing certainly until 2004, were inadequate and that information about risks involved was not shared with clinicians sufficiently promptly and not shared with patients directly until 1997 at the earliest.

Whilst clinicians are typified by Pharmaceutical Manufacturers as 'Learned Intermediaries' who warn patients of risks as part of the consenting process, they can only warn appropriately when themselves properly equipped to warn. Sanofi's approach to collation of the data from Adverse Incidents Reports and the failure to set in train a structured prospective investigation of the reported teratogenic effects of Epilim in the early 1980's, as well as the seeming passivity of the Regulator in failing to require any sort of precautionary action, created a position by the end of the 1980's where the scope of reported but unconfirmed Epilim effects was widening to include malformations and neurodevelopmental delay.

These irreparable effects were much more likely to be relevant to the scope of warning mandated for clinicians by the ***Sidaway*** [29]decision and would certainly be'material' to a patient being warned of risks in the ***Montgomery***[30] sense. [31]

At best, this made warnings about Epilim a trailing indicator probably until 2004; at worst, it may mean that a clinical generation of patients gave consent for treatment on the basis of palpably inaccurate warnings, sufficient to put the basis of those consents in question, if not to vitiate them. Assessed from a ***Montgomery*** standpoint, those are not informed consents and expose the clinicians who obtained them to liability.

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[28] IN-FACT Submission to IMMDS : Datasheets p131; PIL's p135

[29] Sidaway v Governors of the Bethlem Royal Hospital and the Maudsley Hospital (1985) AC 871

[30] Montgomery v Lanarkshire Health Board (2015) AC 1430 : see para 89: " the assessment of whether a risk is material cannot be reduced to percentages. The significance of a given risk is likely to reflect a variety of factors besides its magnitude: for example, the nature of the risk, the effect which its occurrence would have on the life of the patient, the importance to the patient of the benefits sought to be achieved by the treatment, the alternatives available and the risks involved in those alternatives. The assessment is therefore fact sensitive and sensitive also to the characteristics of the patient"

[31]

1990-97

We now set out for ease of reference the evolution of the Datasheet warnings to clinicians, the CSM's 'Current Problems and the PIL warnings to patients during this period taken from the summary produced for the IN-FACT Submission to IMMDS as a commentary upon pages 11-17 of the Sanofi Response to Question 9

C) Datasheet Compendium 1989-1997

ABPI Data Sheet Compendium 1989 – 90

With the Code of Practice for the Pharmaceutical Industry

EPILIM: Sanofi

'Women of childbearing age: Valproic Acid or sodium valproate, like certain anticonvulsants, have been shown to be teratogenic in animals. In women of childbearing age the benefits of these compounds should be weighed against the possible hazard suggested by these findings and their pregnancies should be carefully monitored.' "

Comment

This is the guidance given when the drug was first licensed and takes no account of the widespread reporting of Adverse Incidents following the Rhone Alpes study in 1982. By this time, the clear causation of Neural Tube defects should surely have been reported.

ABPI Data Sheet Compendium 1990 – 91

With the Code of Practice for the Pharmaceutical Industry

EPILIM: Sanofi

'Women of childbearing age: An increased incidence of congenital abnormalities in offspring 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%. Such pregnancies should be carefully screened by alpha-fetoprotein measurement and ultrasound and if indicated amniocentesis.

In all pregnancies monotherapy is to be recommended and the benefits of antiepileptic therapy must be evaluated against the possible risks and patients should be informed of these and the need for screening.

Comment

It is not clear where the figure of 1% is derived from nor is the source upon which this estimate is based. Whilst the risks of treatment should be explained to patients there is no indication as to any alternative treatment. It is not made clear that by this time data suggests that different drugs have different likelihoods of causing abnormalities. Nor is there any guidance about what are the characteristics of 'severe' epilepsy that might justify prescription of Epilim in the first place.

ABPI Data Sheet Compendium 1991 - 92

With the Code of Practice for the Pharmaceutical Industry

EPILIM: Sanofi

'Women of childbearing age: An increased incidence of congenital abnormalities in offspring 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%. Such pregnancies should be carefully screened by alpha-fetoprotein measurement and ultrasound and if indicated amniocentesis.

In all pregnancies monotherapy is to be recommended and the benefits of antiepileptic therapy must be evaluated against the possible risks and patients should be informed of these and the need for screening.

ABPI Data Sheet Compendium 1993 - 94

With the Code of Practice for the Pharmaceutical Industry

EPILIM:
Sanofi Withrop

'Women of childbearing age: An increased incidence of congenital abnormalities (including facial dysmorphia, neural tube defects and multiple malformations) have been demonstrated in offspring born to mothers with Epilepsy both untreated and treated including those treated with Sodium Valproate.

The incidence of neural tube defects in women receiving Valproate neural tube defects in women receiving valproate during the first trimester has been estimated to be in the region of 1%. Pregnancies should be carefully screened by alpha-fetoprotein measurement and ultrasound and if indicated amniocentesis.

In all pregnancies monotherapy is to be recommended and the dosage reviewed. The benefits of antiepileptic therapy during pregnancy must be evaluated against the possible risks and patients should be informed of these and the need for screening.

Comment

Increased definition of Epilim associated effects. Still no clarity over the comparative likelihood of causation of abnormality, between different anti-epileptic drugs. Neither is there any definition of the 'severe' epilepsy for which Epilim should be prescribed.

ABPI Data Sheet Compendium 1994 – 95

With the Code of Practice for the Pharmaceutical Industry

EPILIM:
Sanofi Withrop

*'Women of childbearing age: An inc*reased incidence of congenital abnormalities (including facial dysmorphia, neural tube defects and multiple malformations) have been demonstrated in offspring born to mothers with Epilepsy both untreated and treated including those treated with Sodium Valproate.

The incidence of neural tube defects in women receiving Valproate neural tube defects in women receiving valproate during the first trimester has been estimated to be in the region of 1%. Folate supplementation has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. No direct evidence exists of such effects in women receiving anti-epileptic drugs. However, there is no reason to contra-indicate folic acid in these women.

The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used as abnormal pregnancy outcome tends to be associated with higher total daily dosage.

Women of childbearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy. Pregnancies should be carefully screened by alpha-fetoprotein measurement and ultrasound other techniques if appropriate.

Comment

Still no clarity over the comparative likelihood of causation of abnormality between different anti-epileptic drugs. No definition of 'severe' epilepsy

ABPI Data Sheet Compendium 1995 - 96

With the Code of Practice for the Pharmaceutical Industry

EPILIM:
Sanofi Withrop

'Women of childbearing age: An increased incidence of congenital abnormalities (including facial dysmorphia, neural tube defects and multiple malformations) has been demonstrated in offspring born to mothers with Epilepsy both untreated and treated including those treated with Sodium Valproate.

The incidence of neural tube defects in women receiving Valproate during the first trimester has been estimated to be in the region of 1%. Foliate supplementation has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. No direct evidence exists of such effects in women receiving anti-epileptic drugs. However, there is no reason to contra-indicate folic acid in these women.

The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used as abnormal pregnancy outcome tends to be associated with higher total daily dosage.

Women of childbearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy. Pregnancies should be carefully screened by alpha-fetoprotein measurement and ultrasound other techniques if appropriate.

Comment

No clarity on the comparative safety of Epilim as against other anti-epileptic drugs. No definition of 'severe' epilepsy. No distinction drawn as to the incidence of malformations arising from women treated with anti-epileptic drugs and those untreated.

ABPI Data Sheet Compendium and Summaries of Product Characteristics 1996 -97

With the Code of Practice for the Pharmaceutical Industry

EPILIM:
Sanofi Withrop

*'Women of childbearing age: An inc*reased incidence of congenital abnormalities (including facial dysmorphia, neural tube defects and multiple malformations) has been demonstrated in offspring born to mothers with Epilepsy both untreated and treated including those treated with Sodium Valproate.

The incidence of neural tube defects in women receiving Valproate during the first trimester has been estimated to be in the region of 1%. Folate supplementation has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. No direct evidence exists of such effects in women receiving anti-epileptic drugs. However, there is no reason to contra-indicate folic acid in these women.

The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used as abnormal pregnancy outcome tends to be associated with higher total daily dosage.

Women of childbearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy. Pregnancies should be carefully screened by alpha-fetoprotein measurement and ultrasound other techniques if appropriate.

The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, in divided doses as abnormal pregnancy outcome tends to be associated with higher total daily dosage. Women of child bearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughput pregnancy. Pregnancies should be carefully screened by alpha-fetoprotein measurement, ultrasound and other techniques if appropriate.

Comment

No clarity on the comparative safety of Epilim as against other anti-epileptic drugs. No definition of 'severe' epilepsy. No distinction drawn as to the incidence of malformations arising from women treated with anti-epileptic drugs and those untreated.

See comment on 'Foetal Valproate Syndrome' Paper[32]at p16 of Sanofi response to Question 9 at 'September 1995'. We suggest that information is rather less than explicit.

32

5. Committee on Safety of Medicines

Committee on Safety of Medicines Current Problems in Pharmacovigilance Volume 19 June 1993.

Neural tube defects associated with sodium valproate and carbamazepine – need for Counselling and Screening.

• The use of sodium valproate or carbamazepine in early pregnancy is associated with an increased risk of neural tube defects.

- *Women taking this drug who may become pregnant should be informed of the possible consequences.*
- *Those who wish to become pregnant should be referred to an appropriate specialist for advice.*
- *Women who do become pregnant should be counselled and offered ante-natal screening (alpha-fetoprotein measurement and a second trimester ultrasound scan).*

Committee on Safety of Medicines Current Problems in Pharmacovigilance Volume 23 September 1997

Drug-Induced Birth Defects

'A teratogen is an agent which causes structural or functional abnormalities in the foetus, or in the child after birth. In the UK the proportion of spontaneous abortions in clinically recognised pregnancies is 10-20% and of gross malformations is estimated to be about 3%. The cause of most malformations is not known but at least 2-4% are due to drugs or chemicals.

Known teratogenic drugs

The well-known teratogenic effects of thalidomide provided the main stimulus for the introduction of modern drug regulation, including the Yellow Card Scheme. Other commonly recognised teratogenic drugs include androgens, cytotoxic agents, lithium, retinoids and warfarin. Drugs should only be prescribed in pregnancy if the benefits for both mother and unborn child outweigh the risks. For example, in women with a history of epilepsy, prescription of potentially teratogenic anticonvulsants is often required to prevent seizures, which may be associated with hypoxic CNS damage to the fetus, or in-uterine death. Appendix 4 of the British National Formulary provides a valuable source of information on drugs and pregnancy.

Detecting potential teratogens

During development, drugs undergo studies in animals to assess their potential as teratogens. However, lack of a teratogenic effect in animals does not guarantee safety in human pregnancy. Once a drug is marketed, the Yellow card Scheme is an important method for generating signals which then can be more formally investigated. A further data collection system in the UK is the National Teratology Information Service. This service follows up enquiries regarding patients who have received newly introduced drugs, known or suspected teratogens, or who have been exposed to occupational and environmental chemicals while pregnant, to obtain data on pregnancy outcome.

Assessing Causality

Confirming that a drug is a teratogen may be difficult. Epidemiological studies can provide quantitive estimates of the strength and statistical significance of associations between drug exposure in pregnant women and congenital abnormalities. Such studies were used to

confirm the associations between pre-natal exposure to diethylstilboestrol and vaginal and cervical abnormalities including vaginal adenocarcinoma in female offspring.
Epidemiological studies have several limitations. For example, the maternal disease requiring drug treatment may itself have resulted in the observed association. Spurious associations can occur or important risks may be missed in investigations involving small numbers of affected patients. Furthermore, women who have had a child with a birth defect are more likely to remember the drugs taken during pregnancy than women who have had a normal child. Assessment of the teratogenicity of a drug must be made therefore on the basis of the reproducibility, consistency and biological plausibility of the combined experimental, clinical and epidemiological data.

6. British National Formulary Sodium Valproate/Epilim

The teratogenic effects of valproate in pregnancy was not reported on, in the BNF between the dates of its first licence in 1973 and March 1991.

BNF Number 21 March 1991

Appendix 4: Pregnancy (p478)

Valproate (1, 3):
Increased risk of Neural tube defects (screening advised); neonatal bleeding and hepatotoxicity also reported.

BNF Number 24 September 1992

Appendix 4: Pregnancy. (p516)

Valproate (1, 3)
Increased risk of neural tube defects (screening advised); neonatal bleeding and hepatotoxicity also reported.

Increased risk of Neural tube defects (screening advised); Important: see p216); Neonatal bleeding (related to hypofibrinaemia) and hepatotoxicity also reported. See also Antiepileptics.

P216.
Pregnancy and Breastfeeding:

In view of the increased risk of neural tube and other defects associated, in particular with Carbamazepine, phenytoin and valproate women taking antiepileptic drugs who may become pregnant should be informed of the possible consequences. Those who wish to become pregnant should be referred to an appropriate specialist for advice. Women who become pregnant should be counselled and offered antenatal screening (alpha-fetoprotein measurement and a second trimester ultrasound scan).

To counteract the risk of neural tube defects adequate folate supplements are advised for women before and during pregnancy; to prevent occurrence of neural tube defects, women

should receive folic acid 5mg daily, this dose may also be appropriate for women receiving established antiepileptic drugs.

7. Patient Information Leaflets

Manufacturers became obliged to warn patients of risks in 1990[33]. The PIL's approved by the DHSS in August 1989 were as set out below. No explicit warning of risk was given until 1997 by which time warnings from researchers (if not from Sanofi) encompassed neural tube defects, malformations and neuro developmental delay.[34]

Sanofi - Patient Information Leaflets (taken from contemporary batches)

- Sanofi Winthrop (1995) batch number 305/028.

States:
"a) Are you pregnant or likely to become pregnant?
b) Epilim may affect your condition if you become pregnant and in these circumstances, it is important to consult your doctor promptly. "

- *Sanofi Pharma (1996) batch number 510342.*

States:
"a) Are you pregnant or likely to become pregnant?
b) Epilim may affect your condition if you become pregnant and in these circumstances, it is important to consult your doctor promptly. "

Comment

As leaflets designed to convey information to patients, these fall some way short. They do not explain

- Why you should consult your doctor
- If you do, what information you should give that doctor
- Why the fact of being pregnant might be important
- What risks are being warned of
- Whether the reason to contact your doctor relates to this anti convulsants or all anti convulsants

8. Conclusions on the Evidence Submitted by Sanofi

[33] Medicines Act 1981 (check citation)
[34] For example :.Omtzigt JG, Los FJ, Grobbee DE, Pijpers L, Jahoda MG, Brandenburg H, et al. The risk of spina bifida aperta after first-trimester exposure to valproate in a prenatal cohort: Neurology. 1992;42(4 Suppl 5):119-125 **and** Clayton-Smith J, Donnai D. Fetal valproate syndrome. Journal of medical genetics. 1995;32(9):724-7.

In summary, during this period, patients were reliant upon their treating clinicians (probably neurologists whom they will have seen once a year at best, rather than GP's) for information about the risks of treatment whilst pregnant with Epilim.

Clinicians were reliant upon the warnings published in the Datasheet Compendium or in the British National Formulary for information about risks involved in treating patients with Epilim. These statements of risk appear to have lagged behind research findings because data was slow to accumulate, so that patients will have received from clinicians at best a partial explanation of the risks that they and their baby would be running

There also seems to have been insufficient concern to clarify the difference in incidence of risk of malformation between patients who were treated and those left untreated.

Furthermore, the fact that there was an identifiable difference between the incidence of causation of neural tube defect and malformation by Epilim and its competitor anti epilepsy drugs, is not made clear to clinicians in these annual briefings.

During this period, there are question marks over the adequacy of consents to treatment given by those women undergoing anti convulsant therapy with Epilim.

1997-2004

ABPI Data Sheet Compendium and Summaries of Product Characteristics 1998 - 99

With the Code of Practice for the Pharmaceutical Industry

EPILIM:
Sanofi Withrop

Pregnancy and Lactation: An increased incidence of congenital abnormalities (including facial dysmorphia, neural tube defects and multiple malformations particularly of the limbs) has been demonstrated in the offspring born to mothers with Epilepsy both untreated and treated, including those treated with Sodium Valproate.

The incidence of neural tube defects in women receiving valproate during the first trimester has been estimated to be in the region of 1-2%. Folate supplementation has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. No direct evidence exists of such effects in women receiving anti-epileptic drugs, however there is no reason to contra-indicate folic acid in these women.

The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, in divided doses as abnormal pregnancy outcome tends to be associated with higher total daily dosage. Women of child bearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughput pregnancy. Pregnancies should be carefully screened by alpha-fetoprotein measurement, ultrasound and other techniques if appropriate.

Committee on Safety of Medicines Current Problems in Pharmacovigilance Volume 29 September 2003

'The risk of congenital malformations in infants born to mothers receiving anti-epileptic medications is approximately 2 to 3 times higher than in the general population. An increased incidence of congenital malformations (including facial dysmorphia, hypospadias, and multiple malformations, particularly of the limbs) has been demonstrated in infants born to mother with Epilepsy taking Sodium Valproate.

Two retrospective epidemiological studies have also suggested an association between in-utero exposure to sodium valproate and a risk of developmental delay. Other factors, such as the mother's epilepsy, may also contribute to this risk.

Sodium Valproate is the anti-epileptic of choice in patients with certain types of epilepsy such as generalised epilepsy with or without myclonus or photosensitivity.

Following a review of the available data, including data from the UK Pregnancy and Epilepsy Register, CSM has advised the following:

- *Women of childbearing potential should not be started on sodium Valproate without specialist neurological advice.*
- *Women taking sodium valproate who are likely to become pregnant should receive specialist advice because of the potential teratogenic risk to the fetus.*
- *If taken during pregnancy sodium valproate should be prescribed as monotherapy at the lowest effective dose, in divided does and if possible as a prolonged released preparation.*
- *Folate supplementation prior to pregnancy may reduce the incidence of neural tube defects in infants born to women at high risk. Women should take 5mg folic acid* ***as soon as contraception is discontinued.***

- *Sanofi-Synthelabo (2001) batch number 30504302*

States:
It is known that women who have epilepsy have a slightly higher risk of having a child with an abnormality that other women. Women who have to take Epilim during the first 3 months of pregnancy to control their epilepsy have about a 1-2% chance of having a baby with SPINA Bifida. This however can usually be detected in the first part of pregnancy by normally used screening tests. Taking dietary supplements of folate may lower the risk of having a baby with Spina Bifida. There may also be blood clotting problems in the new born if the mother has taken Epilim during pregnancy. It is therefore essential that you discuss your treatment with your doctor if you are thinking of becoming pregnant or tell your doctor as soon as you know you are pregnant.

9. Expert evidence

We have also followed with interest the expert evidence submitted to the IMMDS Review, and the comments of experts in oral evidence; our comments are as follows.

Professors Clayton-Smith, Turnpenny, Wood and Dr Bromley.

In answer to Question 2 of their composite review they provide a timeline for research based recognition of Sodium Valproate effects as follows:

a) *"Major congenital malformations*

Dickinson et al., (37) and Nau et al., (38) documented early on in its use that VPA crossed the human placenta and was present in higher concentrations in the fetus than in the mother. Throughout the 1980's case reports were published, often as letters to major medical journals, presenting children with a history of VPA exposure and a major congenital malformation, often spina bifida(9, 10, 39-46). In 1982, the first group report came from a French Birth Defect Register and suggested an increased risk of spina bifida associated with VPA exposure(42) which was replicated by birth defect registers in Italy (47) and Spain (48) and then others (49). In their case report to the Lancet in 1989, Oakeshott and Hunt reported three cases of spina bifida from the East Anglian region of the UK and additionally documented that a personal communication from the Committee on Safety of Medicines, indicated that the committee had received 26 such notifications of spina bifida following VPA exposure (50). In addition to this early emerging human data, in their 1986 paper Nau reported that VPA had been demonstrated to be teratogenic in the mouse, rabbit, hamster, monkey(38) suggesting early availability of animal data signalling concern about VPAs teratogenic potential.

From 1983, prospective studies, which followed-up children ascertained during pregnancy, and not just because they had presented with problems, began to be established, and these provided information on risks associated with VPA exposure, which was less subject to ascertainment bias. Early investigations were limited in their reporting as often all AED exposure children were reported as a single group. However, in 1997, a collaboration by a number of European groups was published highlighting an increased association between VPA exposure (n=184) and an increased risk of major congenital malformations (51). For the first time, the issue of a dose dependent relationship was noted; suggesting that doses above 1000 mg daily carried an increased risk for major congenital malformations(51). An interesting cumulative meta-analysis carried out by Tanoshima and colleagues(52) highlighted that this early data was sufficient for certain associated risk with VPA exposure, such as spina bifida, to be demonstrated. This meta-analysis was conducted in a manner by which data was added to the analysis by year of its publication, which clearly shows the accumulation of data over time. Recently, a review of Tanoshima's cumulative meta-analysis has led to the call, that from the 1990s onwards, patients should have been offered alternative treatments and pre conceptual counselling (53). Whilst the authors here agree that the emerging risks associated with VPA treatment should have been more comprehensively and routinely conveyed to patients, the context should be considered. In 1990, lamotrigine (LTG) was not yet licenced in the UK and research to that point, had suggested teratogenic concern regarding phenytoin (PHT), phenobarbital (PB) and primidone (54-56) which were the available alternatives. What disappointingly did not happen at this point was a large programme of research aimed at delineating these risks and understanding them more rapidly. "

Comment

We think that this criticism is balanced and appropriate. There was an evident failure to give patients a proper understanding of the risks associated with Epilim and there was a failure to create, sufficiently early a coordinated programme of research which could explore the

effects of Epilim beyond neural tube defects. This should have included the extent of malformations and the (then) emergent risks of neuro developmental delay.

In stressing the fact that in 1990 (when, by implication, this programme of research should have been begun) Lamotrigine was not yet licensed and those anti convulsant drugs which were, all had teratogenic potential. These authors offer some degree of mitigation for Sanofi's slow disclosure of material risks to patients,but only some.

With the benefit of a degree of hindsight, it can be seen that Epilim's teratogenic potential was greater than the other AED's which might have been a significant distinction to draw in planning such research.

Candour about outcomes was always essential to these warnings. The very real strengths of Epilim as an anticonvulsant drug could be explored in discussion between clinicians and patients, balancing the fact that Epilim was a class leading anti convulsant drug against those outcomes. Only when it became apparent that Epilim's effects were of a different degree than other AED's did this clinical dilemma become possible to resolve by planned pregnancies and providing alternative AED's to women with epilepsy of childbearing age.

Unfortunately, the failure to institute a long-term research programme sufficiently early meant that thelong term solution took far longer to achieve.

The authors also review the timeline for Neurodevelopment, We adopt this timeline and the timeline above in response to the Sanofi timeline Question 9 pp 17-28

b) "Neurodevelopment

The term 'neurodevelopment' refers to a wide range of brain functioning and developmental processes. It covers skills such as reasoning and IQ, language development, and proficiency with motor skills, as well as psychiatric and behavioural diagnoses such as ASD. Children may have a deficit in one area but function well in other areas, or they may have difficulties in a number of areas. The question of whether VPA exposure in pregnancy could cause developmental delay/learning disability first arose in the early case reports where frequently, alongside the description of the malformation there would also be a reference to a poorer developmental profile(6, 44) . Investigations into the health and development of children born to women with epilepsy were underway in Finland (76) and Germany(77) at this time, however they had very few VPA exposed cases, and therefore could not provide clear early evidence. In fact, all of the early studies which looked at development/IQ in the offspring of mothers taking AEDs during pregnancy could be criticised because of inadequate study design, for example analysing all AED exposed children together, or due to the small size of the VPA exposed group. At the turn of the century, research into the neurodevelopment of children exposed to VPA in the womb gained momentum. In a review of 57 children who met the diagnostic criteria for an anticonvulsant syndrome, Moore and colleagues (11) reported that in the children who were school age or older (n= 38), 74% required educational support. Whilst it is unclear how many of these 38 were VPA exposed and therefore had FVS specifically, the majority of the cohort was VPA exposed. A year later in a study by Adab et al., (78), which looked retrospectively at educational outcomes in children born to mothers with epilepsy, it was reported that in those exposed to VPA monotherapy (n = 56), 45% needed additional help in school, which was 3.4 times more likely than unexposed children. The proportion requiring additional school support was also significantly raised in the group exposed to polytherapy that included VPA. In 2002 Dean and colleagues (23) in the North East of Scotland reviewed the medical records of all children with a history of VPA exposure in the womb and found that there were high levels of what they termed 'developmental

delay', with delays most commonly reported in the domains of speech development (29%). In the Dean study, 34% of monotherapy VPA exposed children had either developmental delay or a congenital malformation. Adab and colleagues (79) undertook a follow up to their original study and retrospectively recruited families from the North West where there had been a known exposure to an AED. This study was the first of its size to employ standardised assessment of IQ and therefore had greater precision for identifying cognitive difficulties. In 42 children with VPA exposure the rate of below average IQ was 30% and the mean of the group differed significantly from the untreated group, even after controlling for other influencing variables(79). These studies were retrospective, and there were calls that the samples were highly selective, but importantly they supported the need for further prospective studies examining the neurodevelopmental outcome of children exposed to AEDs including VPA to reduce bias.

Prospective studies were established which improved scientific rigor in terms of recruitment, reduction of certain biases, and statistical approaches. Data from these prospective studies now makes it very clear that children exposed to VPA are at increased risk of a range of neurodevelopmental sequelae. In infancy, children exposed to VPA are delayed in their language and motor development(80). In the NEAD study(32, 33), a prospective follow-up of children born to women with epilepsy who had been treated with a number of different AEDs as monotherapy, and which controlled for confounding factors, demonstrated that the reasoning or IQ of children exposed to VPA (n=49) were up to 9 IQ points lower than that of children exposed to other AEDs; with 37% placed below the average range for their IQ. When the same group of children were reassessed at the age of 6 years similar results were found; the children exposed to VPA continued to have lower reasoning and IQ scores than children exposed to other AEDs (33). IQ is the primary outcome in many studies and an association between VPA exposure and lower IQ has now been reported in a number of prospective studies (26, 27, 30, 33, 34, 81, 82). Not all studies have found this association however (83, 84) but in studies which have failed to demonstrate a difference between the VPA exposed children and control children there appear to be methodological reasons. These include low dose of VPA (83) and a lower than population norm IQ in the control group(84).

Consistent with what is expected for a teratogen, the effects on IQ were shown to be dose-related, with children exposed to higher doses of VPA having lower scores(26, 34). A UK study (26) reported that exposure in the womb to VPA at doses greater than 800 mg daily was associated with a 9.7 point reduction in IQ once other contributing factors had been taken into account by statistical analysis. If the dose of VPA was 800 mg daily or less the associated reduction in IQ points was, on average, reduced to 5.0 IQ points (26). Similarly, dose relationship between the level of valproate exposure and IQ have been found in cohorts from America (32, 33), Australia(34) and Georgia(36); and reflects the clear dose association seen for major congenital malformations reported above.

The data above all comes from studies of groups of children ascertained through a history of VPA exposure and shows that there is an increased risk of poorer IQ associated with VPA exposure.

However, Bromley and colleagues (85) have recently investigated the IQ outcomes in individuals ascertained through a diagnosis of FVS (using the criteria by Dean et al(1). In participants diagnosed with FVSD (both children and young adults), a similar pattern of lower IQ is observed, however the magnitude of difference was far greater in the FVSD population than had been reported from populations with a history of VPA exposure. The discrepancy for IQ, for example, was 19 points different from the expected mean with 52% falling below the average range in comparison to 9% expected to fall within this range based on the

normative sample(85). This demonstrated what has been our clinical experience, that cognitive difficulties are a central feature of FVSD.

The associated impact on the brain from prenatal exposure to VPA appears to have a greater impact on verbal related skills, with studies frequently reporting poorer verbal reasoning skills in comparison to non-verbal reasoning skills (26, 33, 34, 85). Other, non-IQ, cognitive skills have also been demonstrated to be altered by VPA exposure. Children exposed to VPA are more likely to have poorer abilities in their language development (33, 34), aspects of executive functioning skills (33) and in their memory skills(86) in a dose dependent manner. Deficits in the key cognitive skills of reasoning, language, executive and memory functioning, either alone or in combination with each other, are likely to lead to the increased need for educational support noted in the published literature for VPA exposed children. The rates of educational support range from 74% for children with a confirmed FVSD (11, 85) to 37% down to 19% for children exposed higher and lower doses of VPA respectively (26). In a recent population based study, which utilised routinely collected health records and educational outcomes, the children exposed to VPA (n=55) were found to have poorer national examination results for Danish and Mathmatics (87); highlighting the real life impact of the cognitive difficulties.

There has been long-standing concern regarding the diagnosis of ASD in children exposed to VPA in pregnancy. There is a wealth of data from rodent studies which demonstrate an increase in rodent pups displaying ASD type symptomatology following exposure to VPA(88); in fact, the 'valproate autism model' is a frequently utilised tool in autism research(89). Initially individuals reported with ASD were the subjects of single, anecdotal case reports(90, 91) but 6/57 (11%) patients exposed to VPA in the series reported by Moore et al., (11) had ASD. Rasalam et al.,(28) found that the prevalence of ASD in a population of children exposed to AEDs in utero was 8 to 18 times higher that the prevalence of 0.25% calculated for the general population; the prevalence being highest (8.9%) for children exposed to VPA alone. Data from a prospective observational study in the UK reported that the incidence of ASD in the group exposed to VPA monotherapy was around 6%, substantially higher than for other monotherapy groups, and more than seven times higher compared to the control population in which only 0.9% were affected (31, 92). Further strong evidence came from a population study in Denmark by Christensen et al.,(29) in 2013 which demonstrated that the risk of ASD in a

population of children exposed to VPA was more than double that of the general population. However, clinical diagnoses of ASD may only report on the most affected individuals. Wood and colleagues(93) demonstrated that screening for ASD symptoms produced higher levels of difficulties. This is consistent with our clinical experience with FVSD, that many individuals have sub-diagnostic levels of social and communication difficulties but that there is a clear impact on their daily functioning.

An important final observation is that neurodevelopmental difficulties are not restricted to those VPA exposed children with a major congenital malformation. Whilst children with a physical malformation are at a greater risk of having poor IQ scores(26), the exact pattern of reported neurodevelopmental deficits have been demonstrated in three studies which excluded children with major congenital malformations (29, 34, 36).

The majority of data reviewed above comes from individuals exposed to monotherapy VPA. However, similar results across all malformation and neurodevelopmental outcomes are seen for children exposed to VPA in a polytherapy combination(26, 62), compared to exposure to VPA as monotherapy, with the dose of VPA remaining an important mediator of risk. "

Comment

Reading through the list of citations appended to this report it is hard not to be impressed by the sheer volume of research which has been published in this subject during the past ten years from amongst researchers working within a relatively few centres and with a very great deal of co operation.

This has enabled the warning of risks within SmPC's and PIL's to achieve new levels of accuracy and candour, so that for example, a November 2012 PIL[35] recites the following risks about Epilim:

Sanofi Revised (11. 2012.) Batch Number 30514209 815

Epilim Gastro-resistant tablets

Pregnancy and breast-feeding
Women who could become pregnant
You should not take this medicine if you are pregnant or a woman of child bearing age unless explicitly advised by your doctor.
Before you start taking Epilim, your doctor should discuss with you the possible problems when it is taken in pregnancy.

- *Unplanned pregnancy is not desirable in women taking Epilim*
- ***You should use an effective method of contraception and talk to your doctor before planning pregnancy.***

Epilim has no effect on how well the oral contraceptive pill works.

Well before you become pregnant it is important to discuss pregnancy with your doctor and, if you have one, your specialist. This is to make sure that you and your doctor agree that you should have Epilim if you become pregnant.

Women taking Epilim during pregnancy have a higher risk than other women of having a child with an abnormality. The chance of abnormalities is increased if you are also taking other medicines for epilepsy at the same time..

These abnormalities include:

- *Head and face deformities including cleft palate (a gap or depression in the lip)*
- *Deformities of the bones, including hip dislocation*
- *Malformations of the arms and legs*
- *Deformities of the tube from the bladder to the penis, where the opening is formed in a different place*
- *Heart and blood vessel malformations including heart defects*
- *Defects of the lining of the spinal cord*
- *An abnormality of the spinal cord called 'Spina Bifida'*
- *Malformations of the Urethra*

Women who take Epilim during pregnancy may be more likely to have a baby with spina bifida.

[35] See IN-FACT Submission to IMMDS

Taking folic acid 5mg each day as soon as you stop contraception may lower the risk of having a baby with Spina Bifida.

There is also an increased risk of other birth defects. These other defects can usually be detected in the first 3 months of the pregnancy using routine antenatal screening blood tests and ultrasound scans.

Pregnant mothers who take Epilim may have babies with:

- *Blood clotting problems (such as blood not clotting or not clotting very well). This may*

appear as bruising or bleeding which takes a long time to stop

- *Hypoglycaemia (low blood sugar)*
- *Hypothyroidism (underactive thyroid gland, which can cause tiredness or weight gain).*

Some babies born to mother who took Epilim during pregnancy may develop less quickly than normal or have autistic disorders. These children may require additional educational support.

Talk to your doctor before you stop taking Epilim if you want to become pregnant. Do not stop taking Epilim suddenly, as it is likely that your fits will come back.

Women who are planning to get pregnant

If you become pregnant, think you may be pregnant or plan to become pregnant while taking Epilim, you must tell your doctor straight away.

- *Your doctor will give you appropriate counselling and will suggest changes to your treatment or dose*
- *He or she will also want to check your progress while you are pregnant.*
  It is very important that you discuss your treatment with your doctor well before you become pregnant. "

The contrast with the warning from 1990 to 1997 could not be more pointed. In our view this accurate warning should and could have come sooner. How much sooner?

Dr Jeffrey Aronson: By when was there first a testable hypothesis in relation to the teratogenicity of sodium valproate in humans?

The earliest antiepileptic drugs, valproic acid, phenytoin, phenobarbital, primidone, and carbamazepine are all thought to be teratogenic; of these, valproate carries the highest risks, causing about 2% of neural tube defects and an additional increase in major congenital abnormalities of 4–8% [30]. For example, major malformations in infants exposed to carbamazepine or valproic acid monotherapy in utero were analysed in a Swedish nationwide, population-based register study [31]. There were malformations in 35 of 268 valproic acid- exposed infants, of which 28 were severe, and in 46 of 703 carbamazepine-exposed infants, 28 of which were severe. Valproic acid monotherapy compared with carbamazepine monotherapy gave an odds ratio of 3.51 (95% CI = 1.43–4.68) for neonatal malformations. The malformations included neural tube defects, cardiac abnormalities, orofacial clefts, hypospadias, alimentary tract atresia, diaphragmatic hernias, and

craniosynostosis. The authors concluded that the risk of a malformation after exposure to valproic acid is higher than after exposure to carbamazepine.

Teratogenicity of sodium valproate was shown in 1971 in rodents [32] and has been reported in several animal species since then, including primates, albeit in a very small study. The Data Sheet in the Data Sheet Compendium published in 1975 says "This compound has been shown to be teratogenic in animals". Therefore, there was already by that time a testable hypothesis that it would also be teratogenic in humans. Congenital defects associated with drug therapy are regarded as serious adverse effects [33].

A significant signal of teratogenicity in humans was present from 1990 onwards, and by 2005 the evidence for major congenital malformations was overwhelming. Since then the estimated risk ratio and its confidence intervals has remained stable. The latest estimate shows a more than doubling of the risk (RR = 2.24, 95% CI, 2.13 to 2.80) for congenital malformations based on an analysis of over 20 000 subjects.

In 1992, Antman and colleagues used cumulative meta-analysis to show that expert recommendations often lag behind pooled estimates of effect sizes in clinical trials [36]. Thus, it would have been possible after 1992 to have analysed the data on valproate to test the hypothesis that it is not teratogenic.

Comment

This places knowledge of risk of malformation and neurodevelopmental delay some years sooner than reported by Sanofi, and some time before the publication of the CSM's "Current Problems of Pharmacovigilance" paper in September 2003.

10. Knowledge of risk

The central issue from the perspective of the patients is at what point Sanofi and/or the Regulator were aware of the teratogenic effects arising in the children of women with epilepsy who should have been warned of those risks when giving consent to treatment with Epilim

The sequence of discovery of those risks – neural tube defects, other malformations and then neuro developmental delay – is uncontroversial but as detailed above there is a significant delay between identification of those risks and acknowledgement of firstly the possibility and latterly the probability of causative effect.

Patients and some of those experts who have given expert evidence to IMMDS point to an institutional lack of curiosity about these links on the part of both Manufacturer and Regulator until the mid 1990's. The counter arguments to that criticism seem to be that

1. From the Manufacturer's perspective, the Regulator was not requiring such additional research to be undertaken and from the Regulator's perspective, there is was little enthusiasm for additional research which would require very elaborate prospective studies. The Yellow Card scheme of Adverse Incident Reporting allowed a weather eye to be kept – by both Sanofi and the Regulator - on the emerging pattern of adverse events.
2. All AED's seemed to be implicated as having teratogenic effects
3. Even if studies were indicated they were going to be difficult to organise in a rigorous way. Data was more difficult to assemble in an era when computerisation was less advanced than it now is and the studies required to isolate the data which has now

been assembled to prove causation, have benefited hugely from that intervening technological step change.

4. Treatment with Epilim transformed the lives of thousands of patients with seizure control. Many of those who took the drug could for the first time live autonomously; seizure control was of sufficient duration that many were able for the first-time hold driving licenses.

At the same time that that aspect of autonomy was being addressed, another aspect was being neglected: the minority of women prescribed Epilim who were pregnant or who were contemplating pregnancy, who needed to know about risks to their baby: Prompting the questions:

1 At what point can it be argued that the Adverse Incident Reporting about Epilim signalled to the Manufacturer/Regulator the need for clinicians to be advised to restrict the use of Epilim on a precautionary basis to those with otherwise intractable seizures and even in those cases to the minimum dosage consonant with seizure control?

2 At what point can it be argued that Adverse Incident Reporting about other AED's was sufficiently confident to enable clinicians to be able to advocate for epileptic women without intractable seizures, a change of regimen to a drug with fewer/lesser risks?

3 Was the reporting to clinicians by Manufacturer/Regulator via SPC's prior to 2004 sufficiently clear to enable them to make a distinction between those patients who had no choice but to be treated with Epilim and those for whom change to a less teratogenic drug was a treatment option?

Generic causation of injury by the drug is difficult exactly to time. The publication of warnings in SmPC's, PIL's and the prescriber digests like the British National Formulary comes sometime after the raw material of Adverse Incident Reporting has been received, formulated, validated and formalised by the Manufacturer then negotiated over with the Regulator.

Initial 'signals'[36] received from AIR necessarily take time to translate into warnings and there is a potential conflict that arises when they do. Patients need information about risks as soon as those risks seem to have substance, as do the clinicians who advise them, though both these groups have to recognise the need for there to be proper consideration given to verifying signals. This may involve comparison of in house research data – particularly pre-licencing data, data which supported licencing or re-licencing and independent research results; perhaps research not yet fully published but being funded by the Manufacturer.

The potential conflict that arises in these circumstances is that the Manufacturer has an understandable desire not to have to add any more risk warnings to its products than strictly necessary and whilst it owes statutory duties to warn and to agree the terms of such warnings with the Regulator, it has the means (it controls the timetable for doing so and the evidence to justify doing so) as well as the motive for not doing so.

From the Manufacturers perspective Epilim, like all AED's, is a long-term drug. Once a patient was prescribed Epilim and the drug was found to be successful in controlling

[36]3 A 'signal' was defined in 1987 by WHO as/: ''*Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented*''.

seizures, that patient might – in the absence of contraindications - continue to take the drug from teenage years for the rest of her life. Few drugs create such long-term interdependence for patient and Manufacturer as AED's

In the 1980's when pharmacovigilance was less well organised than it now is, when Regulatory standards were not as demanding as they now are and the Regulator had fewer resources to deploy than it now has, it is possible that drug companies, were well positioned to take advantage of this situation. Which may be why it has taken thirty years for the full spectrum of injuries caused by Epilim to be acknowledged.

If the Heneghan/Aronson paper is right that 'signals' about Sodium Valproate should have registered as early as 1992, there is a very considerable concern to be investigated on behalf of patients with injured children, about the failure of the Manufacturer and Regulator to register those signals, and draw the attention of clinicians and patients to those signals.

11. How should a consent to treatment with an AED be sought?

The position post *Montgomery* looks very much more favourable to patients (in its emphasis on individual autonomy and disclosure of material risk) but that decision arises in the context of a single consent to a single intervention rather than a long term treatment with an AED where information about associated risks changes significantly over time.

How does a clinician-reliant for information upon risk warnings given by a Manufacturer, approved by a Regulator- grasp the concerns of a woman with epilepsy contemplating the possibility of pregnancy either immediately or within the foreseeable future, and who wants advice about the best AED for her condition; who in addition wants to be warned about the risks both to herself and any child that she conceives?

US case law makes a distinction for warnings in prescription drug cases– and whilst it sees the Manufacturers warnings of material risk (ie those to which a reasonable patient would be likely to attach significance in deciding whether to take the drug), as appropriately directed to the clinician rather than the patient (rather than as in the EU and UK, directed to both clinicians and patients), the expected warnings must[37]

- indicate the scope of the danger
- communicate the extent or seriousness of the potential danger
- alert a reasonably prudent practitioner to the danger
- be conveyed in a satisfactory manner

and these seem to be components that would not seem controversial in a UK context, save that materiality of risk would be from the patient's perspective and there would be an obligation to offer a perspective on comparative risks of alternative treatments[38]

Consent to long term prescription must differ from the consent given for a single procedure. Consent given by a *Gillick* -competent 14 year old recently diagnosed with seizures, is not the same as that given by a recent graduate in a first job anxious to be able to retain a driving licence only made possible by strict seizure control, nor is the position of a woman in a stable relationship planning a pregnancy similar to these first two examples. But this could be the same woman at different times in her life. So ,there must be a conditional element to

[37] Perez v Wyeth Laboratories Inc. 734A 2d 1245 (NJ1999)

[38] Montgomery :para 89

the consents given at different times with the ability to review a decision when circumstances change.

As in a contract there needs to be certainty as to terms. But once a consent is given there has to be opportunity to review its terms when circumstances change. To do this successfully, both parties to the 'contract' need to be sure that the basis for their agreement is unchanged; if there is a change to that basis brought about by changes in information about risks, then the clinician must be candid about those risks or put the basis of the consent in jeopardy.

Most women taking Epilim will be re prescribed the drug every two months or so by their GP, the original (and subsequent variations in) prescription normally being made by a hospital neurologist whom she might see every eighteen months.

Currently, there is scope to monitor changes in awareness of risk from the PIL distributed in each pack of the drug prescribed and also on the internet but none of those sources of information can constitute the dialogue thought fundamental by *Montgomery* to getting a proper consent.

It seems fair to assume therefore that in the course of a long-term prescription of Epilim an initial consent is given when the drug is first prescribed but at each review with her neurologist, the long term prescribee renews that original consent in the light of her current life circumstances and intentions

The neurologist will have needed to check what changes there were in her medical history and to have updated her in relation to the drug's risk evolving profile which might have involved reduction in dosage or advice to try another AED but however effective a seizure control had been established, this would always have involved consideration of whether or not she was or was planning to be pregnant. The position of the Association of British Neurologists noted above ( ) seems at least until 2014 to have put the utmost emphasis on seizure control and to have seen Epilim as perhaps the most effective of the AED's ; its position until 2016, about its obligations to warn of the risk to a fetus during pregnancy seems to have been less sure . By contrast, few obstetricians would have been in a position to warn confidently of those risks unless seeing a patient who was planning a pregnancy rather than actually pregnant

The neurologist would have been in some difficulty – now alleviated somewhat by the MHRA prescribing guidelines – in giving wholly up to date information because the warnings in BNF, SmPC's and PIL's had been a necessarily trailing indicator but whereas until 2004 or so the information about the drug for the patient in the PIL was inadequate/inaccurate, that position has since noticeably improved.

The neurologist will obviously have had his/her own general knowledge about Epilim but will have only the information made available by the Manufacturer /Regulator to rely upon. Something of a contrast with the position when consenting a patient for an operation. *Montgomery* assumes that the clinician consenting the patient for such procedure, is fully aware of all the information that the patient needs to know to give a fully informed consent from his /her own knowledge and experience.

A physician preparing to consent a patient for initial or continued treatment with Epilim, must be fully aware of the implications of such treatment for a child that his/her patient may

conceive.[39] As well as making an assessment of the patient's need for seizure control and the comparative risks to the patient and her baby of the epilepsy itself. A complex assessment.

So far as Epilim, is concerned, between 1990 and 2010 that was probably not the case for the majority of treating clinicians. So far as the patients themselves were concerned, the PIL's that they would have received between 1997 (when these were first introduced for this drug) and 2004 are likely to have been uninformative or misleading about the risk associated with taking the drug.

For both clinicians and patients, the reported risk profile of the drug reflected the position to the medical standard of proof so far as the Manufacturer and the Regulator were concerned, but that goes back to the question of what to do about 'signals' from Adverse Incident Reporting rather than proof to a medical standard. Particularly, 'signals' that might affect a decision to become pregnant at all or how best to strike a balance between maintaining your own health through seizure freedom and the risks of a pregnancy.

There has been academic debate about how soon a risk should be warned about (in the context of a Product Liability Directive claim), much of it focussing on the **feasibility** of warning. Professor Stapleton[40] argues for a 'scientific consensus of a causal link' formed on the accumulation of enough data to 'sufficiently scientifically significant'. As Richard Goldberg points out[41]this might have the effect of delaying a warning until such time as it could be proved to be statistically significant (i.e. where the relative risk of an association was greater than 2). He is reassured by Stapleton's concession that in some circumstances there may be liability, where there is no warning of a possible adverse effect,

'*even where evidence of a causal link is 'immature''.*

Which seems to suggest that the nature of the risk, as well as its incidence may be relevant to deciding what risks a Manufacturer needs to warn a Patient about and when.

In that formulation the incidence of risk is probably of less significance than the nature of the risk being warned of. A small risk of a serious outcome like malformation or neuro developmental delay in circumstances where:

- the patient wants to become pregnant: or
- wants to be reassured about risks were she accidentally to become pregnant: and
- there may be less risky treatment available

[39] Association of British Neurologists : Submission to IMMDS : December 2018 : ' As neurologists we do not generally advise our patients on contraception….However neurologists would be expected to advise patients and their GP's on the risks of individual AED's in pregnancy…..As adult neurologists, we generally see patients 16 or over so such patients will already have entered puberty – nonetheless the transition of patients with epilepsy from paediatric to adult care is an important for ensuring that appropriate advice has been given. It is important to realise that Valproate would not be a first line agent in a girl entering puberty precisely on account of these risks.

[40] 'Liability for drugs in the US and EU :Rhetoric and Reality' (2007) 27 Review of Litigation 991

[41] 'Medicinal Product Liability and Regulation' Hart (2013) p68

is likely to be material in the *Montgomery* sense of that term. .

Assuming that a 'signal' is something between a first Adverse Incident Report and final confirmation of proof to a medical standard, what obligation to warn arises? Concerns will have been raised with the Regulator as soon as any indication arises, particularly in a category of patient who will not have been involved in pre-licensing testing, which pregnant women would not have been for long established ethical reasons

It is possible with a detailed review of the literature to categorise the strength of 'signals' with some precision. The recent paper from Heneghan and Aronson[42] suggests that using meta-analysis, such signals can be seen to have emerged – perhaps as early as 1992.

12. What more evidence might IMMDS now need?

This Review has produced a wide range of evidence on Sodium Valproate alone as well as overarching information from different clinical, regulatory and compliance bodies. Does it need more help to reach conclusions and recommendations?

It may well be that without publishing formal evidence the Review has had significant help from a wide variety of clinical specialists. Amongst those we anticipate that views may already have been sought from experts in the fields of teratology and pharmacovigilance who would be well able to advise about the speed with which evidence of emergent risks would/should have reached clinicians and patients.

They would also be able to advise about the precautionary attitudes of Regulators in the 1970's and the steps taken to develop pharmacovigilance techniques in the 1980's. An older pharmacovigilance expert might be able to say something about the techniques employed before the digital era.

Organisations which might provide useful and/or comparative information include:

1. **International League against epilepsy**: For a comparative patient based perspective
2. **Government Health Departments information from the USA and EU**: Evidence of risk has been collated from many countries. Where in the world, and when, were concerns first raised? What did they do?
3. **Royal College of Paediatricians:** Might be able to shed light on the likely numbers of affected children What have they done to flag risk, add patients to registries and report suspected effects? What can they do in the future for all presentations to take an holistic approach and contribute to the knowledge about new and existing syndromes? How can they help find those affected?
4. **Epilepsy nurses**: What is their purpose? How do they discuss with patients? How can they help find those affected? General ideas.

[42] Sodium Valproate : Who knew what and when? Cumulative meta analysis gives extra insights' 10.1136 bmjebm-2018-111068

5. **UK Teratology Information Service**: How have they communicated their knowledge to patients, HCPs and regulators? What suggestions do they have for registries? Is Bumps online information being used? How reliable is the information.
6. **Hansard**: How many valproate references in Hansard? There are 89 and 13 for Epilim: Two examples. 1983 Miss Richardson requests public inquiry into valproate related deaths. Geoffrey Finsberg responds no clear evidence of hazard to foetus, 19 deaths associated with VPA but do not indicate causal relationship. No public inquiry required.
7. **No evidence provided on conversations with FDA:** 1985 about VPA psychiatric ADRs and infertility included in FDA data sheets but Ken Clarke responds with not necessary in UK. http://bit.ly/2HjpfJq. These are in addition to the deaths identified in the Parliamentary Questions raised about the case of Heleanor Bye – details of which have been submitted to the Review.
8. **Health economists:** What impact assessments have been done on economic viability of current regulatory system? Cost of ADRs to public finance locally and nationally. What action, chronologically, has been taken by successive governments? Why was Quality Outcome Framework for pre conception counselling retired?
9. **What consideration of Learning disabilities, autism and family carers did DWP** make when redesigning welfare system (eg Universal Credit, Work Capability Assessment, Sanctions, Pensions?)
10. **What externality cost** comprising Benefits payments, Local Authority social care expenditure and Special Education costs have been incurred as a result of this drugs effects since it was licensed?

13. MHRA/DHSC/CMO

Families of FVSD victims believe that the current system for recognising signals is adequate and will prevent this type of tragedy from happening again.

However, this still needs to be explored further as MHRA confirmed in oral evidence clinicians are not widely reporting suspected adverse drug reactions and patients are not fully aware of the Yellow Card scheme, despite now being ,as a group, the most assiduous reporters of pharmaceutical product concerns.

They were unaware of Topiramate currently being scrutinised for teratogenicity.

When formulating policy MHRA says it speaks to the medical profession, views the evidence and then seeks patient opinion. It is this attitude of consulting patients at the end of a process that needs to change. Patients are the evidence.

A patient safety strategy is being developed by DHSC to link patient safety teams in all stakeholders. No evidence has been provided on how patients have been involved in setting the strategy nor what involvement they will have in its implementation.

Whilst the CMO says that ‘messages about new products spreads quickly among clinicians’, emerging evidence on ADRs and new guidance is not sufficiently widely shared. This imbalance needs to be addressed.

We welcome the action taken by the MHRA and their vision of promoting risk minimisation and monitoring of emerging data with patients being an essential part of decision making.

C. Conclusion

All parties involved in this Review need to seek consensus on the management of pharmaceutical and medical device risk and the consequences of inaction in the face of emergent risks.

We believe that regulation of pharmaceutical and medical device regulation should be overtly based on the precautionary principle and should focus on safe healthcare and properly informed understanding of any risks that are inherent in treatment of whatever sort

The development and use of registries and databases for each licensed pharmaceutical and medical device should be fundamental to the development of medical/scientific knowledge and should inform regulatory action, prescription decision making and improved service provision. This needs to be addressed as an urgent priority and made a much more coordinated feature of the relationship between manufacturers, regulators, clinicians and patients.

Appendix A

Pharmaceutical Products Division

Abbott Laboratories
North Chicago, Illinois 60064

Dear Doctor:

RE: PREGNANCY AND VALPROIC ACID (DEPAKENE®)

New data concerning the potential teratogenicity of Depakene have recently been brought to our attention by a Letter to the Editor in The Lancet of October 23, 1982. A review of the same data appeared in a bulletin issued jointly by the Food and Drug Administration and the Centers for Disease Control (CDC) in the Morbidity and Mortality Weekly Report of October 29, 1982.

According to these reports, data collected in the Rhone Valley area of France indicate a higher than normal incidence of spina bifida in the offspring of epileptic mothers who received valproate therapy during the first trimester of pregnancy. Based upon this single preliminary report, the CDC has estimated the risk of valproic acid exposed women having children with spina bifida to be approximately 1.2%. This risk is similar to that for non-epileptic women who have had children with neural tube defects. While no confirmatory data have been found in other birth registries, which may be due to the limited number of valproate exposures evaluable in these populations, we nevertheless feel it appropriate to bring this preliminary report to your attention at this time since there are prenatal counseling centers for women who may have an increased risk of having children with spina bifida.

As you are well aware, the fetus of a pregnant epileptic woman is at an increased risk of serious malformation both as a result of the disease itself and because of various anticonvulsant drugs utilized in treatment. All anticonvulsants carry a warning of potential human teratogenicity in their labeling. Some of these drugs, i.e., phenytoin, trimethadione, paramethadione and valproic acid, have now been associated with increased risk of specific congenital defects.

On the basis of the above mentioned preliminary data, we have made certain revisions in the "Use in Pregnancy" section of our Depakene package insert. A copy of this revised insert is included for your information.

Sincerely,

[redacted]

Medical Director, Medical Affairs

[redacted]

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JCP-F2 CONFIDENTIAL

EXHIBIT 159
WIT:
DATE: 12-3-13
Juliana Zajicek CSR

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ABTPAW001006730

PX 148

(Nos. 5558 and 5687)
09-7278-8102—Rev. Dec., 1982

SPECIMEN

DEPAKENE®

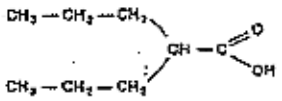
VALPROIC ACID

CAPSULES and SYRUP

WARNING:
HEPATIC FAILURE RESULTING IN FATALITIES HAS OCCURRED IN PATIENTS RECEIVING DEPAKENE. THESE INCIDENTS USUALLY HAVE OCCURRED DURING THE FIRST SIX MONTHS OF TREATMENT WITH DEPAKENE. SERIOUS OR FATAL HEPATOTOXICITY MAY BE PRECEDED BY NON-SPECIFIC SYMPTOMS SUCH AS LOSS OF SEIZURE CONTROL, MALAISE, WEAKNESS, LETHARGY, ANOREXIA AND VOMITING. LIVER FUNCTION TESTS SHOULD BE PERFORMED PRIOR TO THERAPY AND AT FREQUENT INTERVALS THEREAFTER, ESPECIALLY DURING THE FIRST SIX MONTHS.

DESCRIPTION

DEPAKENE (valproic acid) is a carboxylic acid designated as 2-propylpentanoic acid. It is also known as dipropylacetic acid. DEPAKENE has the following structure:



Valproic acid (pK_a 4.8) has a molecular weight of 144 and occurs as a colorless liquid with a characteristic odor. It is slightly soluble in water (1.3 mg/ml) and very soluble in organic solvents.

DEPAKENE is supplied as soft elastic capsules and syrup for oral administration. Each capsule contains 250 mg valproic acid. The syrup contains the equivalent of 250 mg valproic acid per 5 ml as the sodium salt.

CLINICAL PHARMACOLOGY

DEPAKENE is an antiepileptic agent which is chemically unrelated to other drugs used to treat seizure disorders. It has no sedative or anxiolytic potency characteristic of other antiepileptic drugs. The mechanism by which DEPAKENE exerts its antiepileptic effects has not been established. It has been suggested that its activity is related to increased brain levels of gamma-aminobutyric acid (GABA). The effect on the neuronal membrane is unknown.

DEPAKENE is rapidly absorbed after oral administration. Peak serum levels of valproic acid occur approximately one to four hours after a single oral dose of DEPAKENE. The serum half-life of the parent compound is typically in the range of six to sixteen hours. Half-lives in the lower part of the above range are usually found in patients taking other antiepileptic drugs. A slight delay in absorption occurs when this drug is administered with meals but this does not affect the total absorption.

Valproic acid is rapidly distributed and at therapeutic drug concentrations, drug is highly bound (90%) to human plasma proteins. Increases in dose may result in decreases in the extent of protein binding and variable changes in valproate clearance and elimination.

Elimination of DEPAKENE and its metabolites occurs principally in the urine, with minor amounts in the feces and expired air. Very little unmetabolized parent drug is detected in the urine. The drug is primarily metabolized in the liver and is excreted as the glucuronide conjugate. Other metabolites in the urine are products of beta, omega-1, and omega subtraction (C-3, C-4, and C-5 positions). The major acid-drive metabolite in the urine is 2-propyl-2-trans-pentanoic acid; minor metabolites are 2-propyl-glutaric acid, 2-propyl-5-hydroxypentanoic acid, 2-propyl-3-hydroxypentanoic acid and 2-propyl-4-hydroxypentanoic acid.

INDICATIONS

DEPAKENE (valproic acid) is indicated for use as sole and adjunctive therapy in the treatment of simple (petit mal) and complex absence seizures. DEPAKENE may also be used adjunctively in patients with multiple seizure types which include absence seizures.

In accordance with the International Classification of Seizures, simple absence is defined as very brief clouding of the sensorium or loss of consciousness (lasting usually 2-15 seconds), accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

SEE "WARNINGS" SECTION FOR STATEMENT REGARDING FATAL HEPATIC DYSFUNCTION.

CONTRAINDICATIONS

DEPAKENE (VALPROIC ACID) SHOULD NOT BE ADMINISTERED TO PATIENTS WITH HEPATIC DISEASE OR SIGNIFICANT DYSFUNCTION.

DEPAKENE is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS

Hepatic failure resulting in fatalities has occurred in patients receiving DEPAKENE. These incidents usually have occurred during the first six months of treatment with DEPAKENE. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as loss of seizure control, malaise, weakness, lethargy, anorexia and vomiting. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months. However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination. Caution should be observed when administering DEPAKENE to patients with a prior history of hepatic disease. Patients with various congenital enzymatic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk.

The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of drug. The frequency of adverse effects (particularly elevated liver enzymes) may be dose-related. The benefit of improved seizure control which may accompany the higher doses should be weighed against the possibility of a greater incidence of adverse effects.

Usage in Pregnancy: ACCORDING TO RECENT REPORTS IN THE MEDICAL LITERATURE, DEPAKENE MAY PRODUCE TERATOGENICITY IN THE OFFSPRING OF HUMAN FEMALES RECEIVING THE DRUG DURING PREGNANCY. THE INCIDENCE OF NEURAL TUBE DEFECTS IN THE FETUS MAY BE INCREASED IN MOTHERS ASCRIBING VALPROATE DURING THE FIRST TRIMESTER OF PREGNANCY. BASED UPON A SINGLE FRENCH REPORT THE CENTERS FOR DISEASE CONTROL (CDC) HAS ESTIMATED THE RISK OF VALPROIC ACID EXPOSED WOMEN HAVING CHILDREN WITH SPINA BIFIDA TO BE APPROXIMATELY 1.5%. THIS RISK IS SIMILAR TO THAT FOR NON-EPILEPTIC WOMEN WHO HAVE HAD CHILDREN WITH NEURAL TUBE DEFECTS (ANENCEPHALY AND SPINA BIFIDA).

THERE ARE MULTIPLE REPORTS IN THE CLINICAL LITERATURE WHICH INDICATE THAT THE USE OF ANTIEPILEPTIC DRUGS DURING PREGNANCY RESULTS IN AN INCREASED INCIDENCE OF BIRTH DEFECTS IN THE OFFSPRING. ALTHOUGH DATA ARE MORE EXTENSIVE WITH RESPECT TO METHADONE, PARAMETHADONE, PRIMIDONE, AND PHENOBARBITAL, REPORTS INDICATE A POSSIBLE SIMILAR ASSOCIATION WITH THE USE OF OTHER ANTIEPILEPTIC DRUGS. THEREFORE, ANTIEPILEPTIC DRUGS SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING POTENTIAL ONLY IF THEY ARE CLEARLY SHOWN TO BE ESSENTIAL IN THE MANAGEMENT OF THEIR SEIZURES.

ANIMAL STUDIES HAVE ALSO DEMONSTRATED DEPAKENE INDUCED TERATOGENICITY. Studies in rats and human females demonstrated placental transfer of the drug. Doses greater than 45 mg/kg/day given to pregnant rats and mice produced skeletal abnormalities in the offspring, primarily involving ribs and vertebrae; doses greater than 150 mg/kg/day given to pregnant rabbits produced fetal resorptions and (primarily) soft-tissue abnormalities in the offspring. In rats a dose-related delay in the onset of parturition was noted, fetal/neonatal growth and survival of the progeny were adversely affected, particularly when drug administration spanned the entire gestation and early lactation period.

Antiepileptic drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

PRECAUTIONS

Hepatic Dysfunction: See "Contraindications" and "Warnings" sections.

General: Because of reports of thrombocytopenia and inhibition of the secondary phase of platelet aggregation, platelet counts and bleeding time determinations are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving DEPAKENE be monitored for platelet count prior to planned surgery. Clinical evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of DEPAKENE dosage or withdrawal of therapy pending investigation.

Hyperammonemia with or without lethargy or coma has been reported and may be present in the absence of abnormal liver function tests. If elevation occurs, DEPAKENE should be discontinued.

Since DEPAKENE (valproic acid) may interact with concurrently administered antiepileptic drugs, periodic serum level determinations of concomitant antiepileptic drugs are recommended during the early course of therapy. (See "Drug Interactions" section).

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DEPAKENE is partially eliminated in the urine as a keto-metabolite which may lead to a false interpretation of the urine ketone test.

Information for Patients: Since DEPAKENE may produce CNS depression, especially when combined with another CNS depressant (e.g., alcohol), patients should be advised not to engage in hazardous occupations, such as driving an automobile or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

Drug Interactions: DEPAKENE may potentiate the CNS depressant activity of alcohol.

THERE IS EVIDENCE THAT DEPAKENE CAN CAUSE AN INCREASE IN SERUM PHENOBARBITAL LEVELS BY DECREASE OF NONRENAL CLEARANCE. THIS PHENOMENON CAN RESULT IN SEVERE CNS DEPRESSION. THE COMBINATION OF DEPAKENE AND PHENOBARBITAL HAS ALSO BEEN REPORTED TO PRODUCE CNS DEPRESSION WITHOUT SIGNIFICANT ELEVATIONS OF BARBITURATE OR VALPROATE SERUM LEVELS. ALL PATIENTS RECEIVING CONCOMITANT BARBITURATE THERAPY SHOULD BE CLOSELY MONITORED FOR NEUROLOGICAL TOXICITY, SERUM BARBITURATE LEVELS SHOULD BE OBTAINED, IF POSSIBLE, AND THE BARBITURATE DOSAGE DECREASED, IF APPROPRIATE.

Primidone is metabolized into a barbiturate and, therefore, may also be involved in a similar or identical interaction.

THERE HAVE BEEN REPORTS OF BREAKTHROUGH SEIZURES OCCURRING WITH THE COMBINATION OF DEPAKENE AND PHENYTOIN. MOST REPORTS HAVE NOTED A DECREASE IN TOTAL PLASMA PHENYTOIN CONCENTRATION. HOWEVER, INCREASES IN TOTAL PHENYTOIN SERUM CONCENTRATION HAVE BEEN REPORTED. AN INITIAL FALL IN TOTAL PHENYTOIN LEVELS WITH SUBSEQUENT INCREASE IN PHENYTOIN LEVELS HAS ALSO BEEN REPORTED. IN ADDITION, A DECREASE IN TOTAL SERUM PHENYTOIN WITH AN INCREASE IN THE FREE VS. PROTEIN BOUND PHENYTOIN LEVELS HAS BEEN REPORTED. THE DOSAGE OF PHENYTOIN SHOULD BE ADJUSTED AS REQUIRED BY THE CLINICAL SITUATION.

THE CONCOMITANT USE OF VALPROIC ACID AND CLONAZEPAM MAY PRODUCE ABSENCE STATUS.

Caution is recommended when DEPAKENE (valproic acid) is administered with drugs affecting coagulation, e.g., aspirin and warfarin. (See "Adverse Reactions" section).

There have been reports of altered thyroid function tests associated with DEPAKENE. The clinical significance of these is unknown.

Carcinogenesis: DEPAKENE was administered to Sprague Dawley rats and ICR (HA/ICR) mice at doses of 0, 50 and 150 mg/kg/day for two years. Although a variety of neoplasms were observed in both species, the chief findings were a statistically significant increase in the incidence of subcutaneous fibrosarcomas in high dose male rats receiving DEPAKENE and a statistically significant dose-related trend for benign pulmonary adenomas in male mice receiving DEPAKENE. The actual incidence of fibrosarcomas in male rats was low with only two low dose and five high dose animals being affected. The presence of these tumors is not considered to be drug-related or of biological significance for the following reasons: (1) the overall low incidence, (2) the published variable incidence of spontaneously occurring fibrosarcomas and pulmonary adenomas in rats and mice respectively, (3) the long latency period of the neoplasms and (4) the fact that statistical significance of tumor incidence was present in males only. The significance of these findings for man is unknown at present.

Mutagenesis: Studies on DEPAKENE have been performed using bacterial and mammalian systems. These studies have provided no evidence of a mutagenic potential for DEPAKENE.

Fertility: Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at doses greater than 300 mg/kg/day in rats and greater than 90 mg/kg/day in dogs. Segment I fertility studies in rats have shown doses up to 350 mg/kg/day for 60 days to have no effect on fertility. THE EFFECT OF DEPAKENE (VALPROIC ACID) ON THE DEVELOPMENT OF THE TESTES AND ON SPERM PRODUCTION AND FERTILITY IN HUMANS IS UNKNOWN.

Pregnancy: See "Warnings" section.

Nursing Mothers: DEPAKENE is excreted in breast milk. Concentrations in breast milk have been reported to be 1-10% of serum concentrations. It is not known what effect this would have on a nursing infant. Caution should be exercised when DEPAKENE is administered to a nursing woman.

ADVERSE REACTIONS

Since DEPAKENE (valproic acid) has usually been used with other antiepileptic drugs, it is not possible, in most cases, to determine whether the following adverse reactions can be ascribed to DEPAKENE alone, or the combination of drugs.

Gastrointestinal: The most commonly reported side effects at the initiation of therapy are nausea, vomiting and indigestion. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps and constipation have been reported. Both anorexia with some weight loss and increased appetite with weight gain have also been reported.

CNS Effects: Sedative effects have been noted in patients receiving valproic acid alone but are found most often in patients receiving combination therapy. Sedation usually disappears upon reduction of other antiepileptic medication. Ataxia, headache, nystagmus, diplopia, asthenia, "green before eyes", tremor, dysarthria, dizziness, and incoordination have rarely been noted. Rare cases of coma have been noted in patients receiving valproic acid alone or in conjunction with phenobarbital.

Dermatologic: Transient increases in hair loss have been observed. Skin rash and petechiae have rarely been noted.

Psychiatric: Emotional upset, depression, psychosis, aggression, hyperactivity and behavioral deterioration have been reported.

Musculoskeletal: Weakness has been reported.

Hematopoietic: Thrombocytopenia has been reported. Valproic acid inhibits the secondary phase of platelet aggregation. (See "Drug Interactions" section). This may be reflected in altered bleeding time. Bruising, hematoma formation and frank hemorrhage have been reported. Relative lymphocytosis and hypofibrinogenemia have been noted. Leukopenia and eosinophilia have also been reported. Anemia and bone marrow suppression have been reported.

Hepatic: Minor elevations of transaminases (e.g., SGOT and SGPT) and LDH are frequent and appear to be dose related. Occasionally, laboratory test results include, as well: increases in serum bilirubin and abnormal changes in other liver function tests. These results may reflect potentially serious hepatotoxicity. (See "Warnings" section).

Endocrine: There have been reports of irregular menses and secondary amenorrhea occurring in patients receiving DEPAKENE.

Abnormal thyroid function tests have been reported. (See "Precautions" section).

Pancreatic: There have been reports of acute pancreatitis occurring in patients receiving DEPAKENE.

Metabolic: Hyperammonemia. (See "Precautions" section).

Hyperglycinemia has been reported and has been associated with a fatal outcome in a patient with preexistent nonketotic hyperglycinemia.

OVERDOSAGE

Overdosage with valproic acid may result in deep coma.

Since DEPAKENE is absorbed very rapidly, the value of gastric evacuation will vary with the time since ingestion. General supportive measures should be applied with particular attention being given to the maintenance of adequate urinary output.

Naloxone has been reported to reverse the CNS depressant effects of DEPAKENE overdosage. Exchange transfusion could theoretically also reverse the antiepileptic effects of DEPAKENE in should be used with caution.

DOSAGE AND ADMINISTRATION

DEPAKENE (valproic acid) is administered orally. The recommended initial dose is 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day, until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 60 mg/kg/day. If the total daily dose exceeds 250 mg, it should be given in a divided regimen.

The following table is a guide for the initial daily dose of DEPAKENE (valproic acid) 15 mg/kg/day:

Weight (kg)	Weight (lb)	Total Daily Dose (mg)	Number of Capsules or Teaspoonfuls of Syrup (Dose 1	Dose 2	Dose 3)
10-24.9	22 - 54.9	250	0	0	1
25-39.9	55 - 87.9	500	1	0	1
40-54.9	88 - 121.9	750	1	1	1
55-74.9	122 - 164.9	1,000	1	1	2
75-89.9	165 - 197.9	1,250	2	1	2

The frequency of adverse effects (particularly elevated liver enzymes) may be dose-related. The benefit of improved seizure control which may accompany the higher doses should therefore be weighed against the possibility of a greater incidence of adverse reactions.

A good correlation has not been established between daily dose, serum level and therapeutic effect, however, therapeutic serum levels for most patients will range from 50 to 100 mcg/mL. Occasional patients may be controlled with serum levels lower or higher than this range.

As the DEPAKENE dosage is titrated upward, blood levels of phenobarbital and/or phenytoin may be affected, (See "Precautions" section).

Patients who experience G.I. irritation may benefit from administration of the drug with food or by slowly building up the dose from an initial low level.

THE CAPSULES SHOULD BE SWALLOWED WITHOUT CHEWING TO AVOID LOCAL IRRITATION OF THE MOUTH AND THROAT.

HOW SUPPLIED

DEPAKENE (valproic acid) is available as orange-colored soft gelatin capsules of 250 mg valproic acid in bottles of 100 capsules (NDC 0074-6681-13), in ABBO-PAC® unit dose packages of 100 capsules (NDC 0074-6681-11), and as a red syrup containing the equivalent of 250 mg valproic acid per 5 ml as the sodium salt in bottles of 16 ounces (NDC 0074-6682-16).

REFERENCES

1. Robert E., Guibaud, P. Maternal Valproic Acid and Congenital Neural Tube Defects, *The Lancet*, 2(8304):837, 1982.
2. Centers for Disease Control. Valproic Acid and Spina Bifida: A Preliminary Report — France, *Morbidity and Mortality Weekly Report*, 31(12): 845-846, 1982.

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Components of a Fetal Valproate Spectrum Disorder Trust ('FVST')

Assuming that a suitable proposal for redress were to be forthcoming at the end of the IMMDS process, how could such a proposal be implemented?

1. Trust Company Limited by Guarantee

As well as registering as a UK charity – with clearly defined charitable objectives - , establishing a new Trust as a Company Limited by guarantee, provides an independent body investing the capital fund, distributing funds to beneficiaries and maintaining a rolling review of needs over the lifetime of the Trust.

The structure imposes Trustee obligations without exposing Trustees to excessively onerous personal liability. Placing funds within a Trust in this way isolates them from political influence and/or Civil Service inertia

2. Scrutiny of the Trust

Funds coming from Government or Private Sector sources to compensate victims of FVSD are likely to be hard won and there will be concern for continuing scrutiny to ensure that they are not dissipated.

Funds in such a Trust will be subject to a formal independent annual audit, and in addition an obligation to make an annual written report to the House of Commons Health Select Committee, (upon which the Chair of Trustees might be invited by the Committee to answer oral questions).

3. Membership of Trustee Board

The roles which the Trust will be asked to fulfil over time imply that there will be a need for a skills-based Board including Trustees with Legal, Financial and Medical expertise. The experience of other Trusts (particularly the vCJD Trust) suggests that parental Trustees may have an important role to play once their own claims on Trust funds for direct loss have been resolved. However consideration should be given to any potential conflicts of interest.

The capacity for teething troubles in setting up such a Trust, during the initial task of identifying claimants' entitlement to be compensated and in dealing with reports to the

Health Select Committee, suggests that a High Court Judge with experience of personal injury work might be an appropriate Chair, at least in the Trust's early years.

4. CEO and staff

The appointment of the CEO is the most critical of all appointments in this scenario because of the enormous task of implementing the strategy of the Trust Board in meeting the needs of the FVSD beneficiaries.

The likely **number** of those beneficiaries; their **age range** (small children to middle aged people); thus the **duration** of the Trust; the job of implementing meaningful redress in line with the Trust Deed for that very disparate group; and, of managing the staff carrying out the financial management and needs based response to beneficiaries, (who having campaigned so long for compensation and are likely to be a vociferous community to serve) will be a challenging role even for someone experienced in this field.

In addition, there will be a need for the Trust to liaise with clinicians at the **Regional Centres** established to support patients with FVSD and with researchers exploring the extent of harmful effect of Sodium Valproate upon the children of epilepsy sufferers.

It is also recognized that the Regional Centres will have a significant role in beneficiary ascertainment and in defining responses for beneficiaries to evolving support needs.

5. Terms of the Trust

For the purposes of this paper, it is assumed that there is a consensus that a scheme of compensation should be implemented and that a suitably funded Trust will need to be established. The first task is to find out how much will have to be earmarked to meet needs and over what timescale. The experience of the Thalidomide Trust suggests that in establishing the size of the fund it is important to ensure that:

- From the outset, provision is made for there to be sufficient funds so that once the Trust is established, there can be immediate interim payments made to beneficiaries once their diagnosis is confirmed and also a capital fund for investment by the Trustees (at their discretion) intended to enable annual payments to be made to beneficiaries to meet continuing needs. Such a fund should pursue a policy of ethical investment;

- The Trust is structured so that any payments made by the Trust are received tax free by its beneficiaries;
- There is provision for regular review of the evolving needs of the beneficiaries, so that the Trust has a clear understanding of the pattern of those needs of its beneficiaries and of the costs implications for forward financial planning of those needs. These Reviews should be aligned with important points of transition for Beneficiaries, (e.g. leaving secondary education and preparing for retirement);
- This should lead to an overall review of the Trust's financial needs every five years; so that the compensators can be required at that review to top up the Trust's resources if necessary;
- Any money received by beneficiaries from the Trust does not affect their entitlement to means-tested State Benefits or statutory-funded services (such as social care and specialist education). The three Support Groups who have reviewed this proposal are emphatic about the importance of this provision

The conventional wisdom of these sort of Trusts is that the sum to be offered to compensate is established between the compensators and the claimants' representatives in a negotiation in which the numbers likely to be compensated and the estimated quantum of likely needs (made up of care costs to date, continuing and future care costs as well as lost earnings) are factors.

Maintaining eligibility for and full access to State Benefits, Local Authority Social Care Support and Special Education provision is a crucial part of the exercise, so that receipt of payments, does not distort the meeting of present needs from both Trust sourced periodical payments and benefit entitlements.

It is assumed that any fund established will in part compensate with lump sums (to meet the capitalised costs of historic care or of adapted housing) and in part make annual periodical payments to meet current identified needs. There will need to be a distinction maintained between awards to mothers for care given to date and their own pain suffering and loss of amenity and awards to children for the impact of lifelong injuries and consequential care, housing and equipment needs.

The likely number of beneficiaries of this Trust, the task of ascertaining those numbers and of their interim and then annual needs as well as the task of continuing review of those needs over the period of the beneficiaries' lifetimes, implies a significant level of staffing to

meet those needs and a significant annual administrative cost to do so .Anecdotal evidence suggests a high percentage of beneficiaries who either now lack capacity or may never achieve capacity when of age ; annual administrative costs should therefore budget for significant costs arising from the involvement of the Court of Protection in managing the needs of incapacitated beneficiaries

As a comparison, to meet the needs of 464 Thalidomiders, the Thalidomide Trust currently has a staff of 16 (Full Time Equivalent 13.7) with a wide range of skills/expertise.

6. Determining entitlement to be compensated

Children entitled to be compensated will have to show that their mothers were treated with Sodium Valproate during pregnancy and that they demonstrate symptoms of Fetal Valproate Spectrum Disorder('FVSD').

An expert group will have to be convened to confirm diagnostic criteria for this condition so as to define admission to the Trust's beneficiary group and to provide a basepoint to enable Trustees to determine extent of injury and entitlement to compensation

As matters stand there are children who already have such a diagnosis having been assessed for admission to the Fetal Anti Convulsant Litigation ('FACL') or having attended existing centres with specialist expertise where a confident diagnosis has been reached: However, there is believed to be a significant degree of under diagnosis of this condition.

In addition, therefore to the existing children with an established diagnosis, it is proposed that a research project be undertaken at the 23 genetic centres in the UK, to identify current and historic array testing pointing to FVSD and a review of medical records to establish maternal ingestion during pregnancy of Sodium Valproate to identify the likely scale of the previously unidentified FVSD cohort.

Such a study would need to be conducted by a single group of researchers, working with local consultant geneticists to review and confirm suspected cases. The study would need to be properly costed and funded and would need to have a Multi Centre Research Ethics Committee approval. It is thought that the study itself could be undertaken in roughly six months after achieving such Research Ethics Committee approval.

This study would only identify those affected by FVSD who had been referred for genetic assessment; there is probably a further group of sufferers who have not been referred.

Publicising the fact of the research exercise amongst paediatricians and GP's might lead to the identification of another cohort. Since the drug has been licensed since the mid 1970's, it seems likely that there will be patients who have remained undiagnosed for some/many years.

The practical effect of this staged diagnosis should be that there is a group who could be eligible for some initial compensation immediately, a further group for whom entitlement could be established within say nine months and a third group whose eligibility might take between 9-18 months to establish.

It would obviously be better to be able to identify immediately how many people need to be compensated so as to make an immediate overall estimate of the likely cost of compensating that group which could be agreed with the compensators, but efforts to define this group have not been necessary until now. Accordingly, this ascertainment time will be a necessary element of the overall timescale in implementing any compensation Trust.

There may also be some additional cases of FVSD emerging over the next few years despite the strictures on prescription of Sodium Valproate for women with epilepsy of childbearing age and the Pregnancy Prevention Programme.

Clinical opinion will also be needed to provide an agreed categorisation of the severity of impact of the FVSD in each case, particularly in identifying those cases in which patients lack capacity and are always likely to do so, both because those cases are likely to have the widest range of needs to be met by the Trust and also because their financial affairs and medical treatment and broader health and wellbeing support will need to be managed by the Court of Protection.

There is a consensus among the Support Groups that the present definitions of injury caused by FVSD must not be regarded as closed. As new research yields results, any new forms of injury identified should be accepted by the Trustees as entitling a Beneficiary to compensation

The Trust will also need to have the power to constitute, as soon as practicable, a representative group from amongst the beneficiaries to enable them to contribute to the work of the Trust.

7. Operation of the Trust

Trust Board

Meetings four times a year and setting strategic direction for the main functions and work streams of the Trust, namely **Finance** (investment decisions, audit, beneficiary payments and day to day cash flow planning), **Ascertainment** Committee (ascertaining those who will be the Trust's beneficiaries) and **Health** (liaison with Regional FVSD Centres, review of existing beneficiary status, ensuring the needs of beneficiaries are understood and met in order to maximise their independence and quality of life, supporting beneficiaries with the most complex needs and providing tailored information resources – including a website)

Attendance by Trustees, CEO, Finance and Health Directors

Finance, Ascertainment and Health Committees are sub committees of the Board and meet between two and four times a year, with a combination of Trustee) and Staff members, to implement strategic direction; CEO attends all these meetings. Ascertainment Committee will need to meet as required to assess new claims, over time its meetings will become less frequent as a wider group of beneficiaries is identified

Staff groupings mirror these areas of expertise with a Finance Director heading the Finance team, Health & Wellbeing Director the health and wellbeing team and the day to day dealings with the beneficiaries dividing along the lines of whether it is finance or a health and wellbeing enquiry.

Continuing Needs Assessments on a three year cycle should be the joint responsibility of the Finance and Health Sub Committees and should involve one to one meetings with beneficiaries

Investment in an appropriate IT infrastructure will be essential to capture data on current and emerging needs.

Close liaison with Clinical research groups (as well as the Regional FVSD Centres) throughout the UK and/or internationally will be essential to inform the Trust's ongoing work. It may be appropriate, from time to time for the Trust to commission research into aspects of the effects of FVSD which have a bearing on the ability of the Trust to carry out its work in supporting its beneficiaries. The Support Groups believe that whilst this power is appropriate, the proposed Trust should not be a primary source of research funding for academic/clinical researchers in this field.

8. Location:

FVSD is a UK wide problem and thus location in London is not essential.

The leading research group in the country is located in Manchester/Liverpool which might predispose to locating the office in NW England. Good transport links for Trustee and Finance, Health and Claims Committee meetings are essential, as well as for staff recruitment

Location in Manchester might emphasise that the proposed Trust is a UK wide rather than London-centric body, it may also reduce administration costs.

Proposal drafted by and with the support of:

Mr David Body
Leigh Day Solicitors
FACSaware
OACS Charity
Valproate Victims

10.7.2019

OACS Ireland

OACS Ireland shared the following with the Review Team at, and in support of, the Oral Hearing in May:

- Datasheets: Epilim 1974; Epilim Chrono 2001; Depakine 2006 (France); Epilim Chrono 200 CR 2008;
- Patient Information Leaflet: Epilim Chrono 2001; Epilim Chrono CR 2004
- Product Authorisation (Ireland): Epilim 1975; Epilim 1980; Epilim 200mg 1983
- Publications:
    - Workshop on Antiepileptic Drug Development, April 15 1977. Summary, Tables and Appendices. Commission for the Control of Epilepsy and its Consequences. U.S. Department of Health, Education, and Welfare. U.S.A.
    - Extract from: The Food and Drug Administration's Process for Approving New Drugs: Oversight : Hearings Before the Subcommittee on Science, Research, and Technology of the Committee on Science and Technology, U.S. House of Representatives, Ninety-sixth Congress, First Session, June 19, 21, July 11, 1979 (p95)
    - Thesis: Richard H. Finnell (1980) The Fetal Hydantoin Syndrome: An Animal Model. Department of Medical Genetics. University of Oregon Health Sciences Center.
    - FACS Forum Ireland Submission to the Joint Committee on Health 25th April 2018 ‘Foetal Anti-Convulsant Syndrome (FACS) and the use of Sodium Valproate in Ireland’
    - OACS Ireland paper reviewing evidence submitted to the Review
    - Blotière, PO et al. Risks of 23 specific malformations associated with prenatal exposure to 10 antiepileptic drugs (2019) Neurology 93:e1-e14. doi:10.1212/WNL.0000000000007696
    - Barton, S., Nadebaum, C., Anderson, V. A., Vajda, F., Reutens, D. C., & Wood, A. G. (2018). Memory dysfunction in school-aged children exposed prenatally to antiepileptic drugs. Neuropsychology, 32(7), 784-796. http://dx.doi.org/10.1037/neu0000465
    - Bromley et al. (2019) Intellectual functioning in clinically confirmed fetal valproate syndrome. Neurotoxicology and Teratology 71: 16–21
    - ANSM (2019) Antiépileptiques au cours de la grossesse: Etat actuel des connaissances sur le risqué de malformations et de troubles neuro-développementaux. Synthèse. April 2019. *English translation provided.*
    - Schardein, James L. (2000) Chemically Induced Birth Defects. 3rd Edition. Marcel Dekker, Inc. New York. Basel.
    - Committee on Safety of medicines (1983) Current Problems Number 9. January 1983. Sodium Valproate (Epilim) and congenital abnormalities.

Professor Carl Heneghan

Professor of Evidence-Based Medicine, University of Oxford

Received 28/03/2019

For the attention of the MHRA, the IMMDS review team, the APPG Primodos and interested parties,

The attached letter sets out our response to questions raised for the first time during the MHRA meeting on the 18th March. We have set out our detailed response to criticisms of our review in this report.

We also present a pooled analysis of data that were included in the report of the UK's Commission on Human Medicines independent Expert Working Group (EWG) [2], based on data obtained through an FOI request.

In terms of point A in our report. A Critical appraisal of the Heneghan et al. systematic review, we have set out the issues on

1. The selection of controls.
2. The selection of confounding variables across studies.
3. The analysis from studies that took account of a previous history of congenital malformations.

Point B, sets out the Meta-analysis results based on the EWG report data obtained through an FOI request.

Table 2 shows the striking similarity of the results for the EWG review and the Heneghan et al review for congenital heart defects, any malformations, and urogenital malformations.

This finding further adds to strengthen our conclusions as both systematic reviews show that the use of oral HPTs in pregnancy is associated with increased risks of congenital malformations.

We welcome the opportunity to respond to further criticisms and undertake any further analysis as requested.

A copy of this reports is available at: https://www.cebm.net/update-ohpts/

A copy of the protocol is available at: Hormone pregnancy test use in pregnancy and risk of abnormalities in the offspring: a systematic review protocol. CEBM https://www.cebm.net/2o019/03/hpt-protocol/

Attachment: Update to the association between Oral Hormone Pregnancy Tests, including Primodos, and congenital abnormalities

Update to the association between Oral Hormone Pregnancy Tests, including Primodos, and congenital anomalies

Carl Heneghan, Jeffrey K Aronson

On 18 March 2019, C Heneghan and JK Aronson discussed the findings of the Heneghan et al systematic review “Oral hormone pregnancy tests and the risks of congenital malformations: a systematic review and meta-analysis” [1] at a meeting of an ad hoc expert group convened by the Medicines and Healthcare products Regulatory Agency (MHRA) in London.

The meeting sought to assess the suitability and robustness of the methods used, including the selection and application of the quality scores and any clinical implications.

Because we had inadequate time to respond to questions raised for the first time during the meeting, we have set out our detailed response to criticisms in this report. We also present a pooled analysis of data that were included in the report of the UK’s Commission on Human Medicines independent Expert Working Group (EWG) [2], based on data obtained through an FOI request.

A. Critical appraisal of the Heneghan et al. systematic review

On 5 March, we were sent the MHRA’s review of the Heneghan et al systematic review. [1] The questions raised about the review were:

4. The selection of controls.
5. The selection of confounding variables across studies.
6. The analysis from studies that took account of a previous history of congenital malformations.

1. Selection of controls

Of the 16 case-control studies, Heneghan et al did not include data for 40 participants from two studies in which there was the potential to select an alternative group for comparison. Therefore, 40 of 17,194 available items of patient data (0.23%) were not included in the analysis.

These 40 items came from two of the 26 studies:

- in Ferencz 1980, 20 disease controls were not included in the analysis because none had used hormone pregnancy tests;
- in Greenberg 1977, 20 subjects were reported as having been exposed to hormones in both the case and control groups, and we considered it likely that these were exposed twins or family members.

Of the 10 cohort studies, we did not include data from 3132 subjects from 4 studies in which an alternative group could have been selected for comparison. Therefore 3132 of the 55,974 items of patient data (5.61%) were not included in the analysis.

These 3132 items came from four of the 26 studies:

- in Fleming 1978, we excluded 140 doubtful malformations, which were mostly rhesus incompatibility (n = 37) and stillbirths (n = 100);
- in Michaelis 1983, we excluded 108 patients who had been exposed not only to Duogynon but also to other hormones;
- in Rumeau-Rouquette 1978, we excluded 1224 patients in whom other estrogen-progestogen derivatives were used that were not hormone pregnancy tests;
- in Torfs 1981, we excluded patients in whom serum tests (n = 689) or urine tests (n = 332) had been used; we included 17,057 non-affected controls.

Thus, Heneghan et al used 95.7% (69,996/73,168) of the available control data. The main reasons for omitting the rest were non-use of hormones or other tests or, as set out in our protocol (computer dated 23 October 2018), we extracted data for the controls that were most closely matched to the cases. The exclusion of 4.33% of the control data had minimal impact on the effect estimate and does not remove the statistical significance.

Protocol: Hormone pregnancy test use in pregnancy and risk of abnormalities in the offspring: a systematic review protocol. Carl Heneghan, Elizabeth Spencer, Bennett Holman, Igho Onakpoya. 25 March 2019. CEBM https://www.cebm.net/2o019/03/hpt-protocol/

2. Selection of confounding variables across studies

Confounding variables for matching were reported in 19 of the 26 studies (see Table 1). As we described in our paper, we consider that of the 16 case-control studies, 12 controlled for the most important factor (item 5a in the Newcastle-Ottawa Scale, NOS for non-randomized studies) and nine controlled for important additional factors (item 5b). Of the ten cohort studies, six controlled for the most important factor (item 5a) and four controlled for important additional factors (item 5b). Table 1 sets out the confounding variables collected and notes on matching/adjustments made in each individual study.

“A further assessment of bias in studies of harms: a case study of Primodos and congenital malformations” is set out in BMJ EBM Spotlight (published 15 March). This post discusses in detail the assessment of quality in assessing associations of harms and the use of the NOS.

Heneghan C, Assessing bias in studies of harms: a case study of Primodos and congenital malformations. 15 March 2019.

BMJ EBM Spotlight.: Assessing bias in studies of harms: a case study of Primodos and congenital malformations

https://blogs.bmj.com/bmjebmspotlight/2019/03/15/assessing-bias-in-studies-of-harms-a-case-study-of-primodos-and-congenital-malformations/

3. Analysis of the data from studies that took account of a previous history of congenital malformations

Two studies took account of a previous history of congenital malformations in their analysis:

Gal et al. 1972: Excluding cases of previous malformed babies and those with a history of infertility did not affect the statistical significance: cases 15/85 vs control 4/97 (P = 0.01 to 0.001).

Greenberg et al. 1977: After exclusion of all case-control pairs with a family history of congenital malformations in either or both families, use of HPTs by case mothers remained statistically significant: cases 64/743 vs control 35/781 ($\chi^2 = 9.42$; $P < 0.01$). Cases and controls were matched for all factors, except a history of previous offspring with abnormalities in the study families.

B. Meta-analysis of results presented in the EWG report

1. Obtaining the raw data extracted by the EWG

After discussions of the APPG on 21 January 2019, Marie Lyon sent an FOI request to the MHRA on 30 January 2019, asking them to release the raw data from the EWG report (see exhibit 1); she wrote again on 4 February 2019.

"The APPG supporting the Association have put in an FOI request for the raw data used in the Forest plot conclusions. I was not aware this information was excluded in the EWG document. Would you please ask the MHRA/CHM why the raw data was not included and would you also please ask them to expedite the request for this information. The EWG pledged to allow 'full public scrutiny and to publish all evidence which had been gathered, together with the assessments of the data.' Exclusion of the raw data does not fulfil this pledge."

She received a response on 6 February: "the request will be forwarded to the appropriate department". A copy of the FOI request was sent to IMMDS on 20 February. The issue of the availability of the raw data was raised by Lord Alton in the House of Lords on 28 February. On 5 March, the IMMDS emailed Marie Lyon to ask if the FOI request had been actioned. She confirmed that it had not.

Marie Lyon sent a further request on 6 March: *"Would you please let me know if the raw data I requested has been actioned yet."* She received a response from the MHRA on 8 March, but this did not include the attachment containing the raw data. On 8 March, she asked for the attachment and finally received the raw data on 11 March.

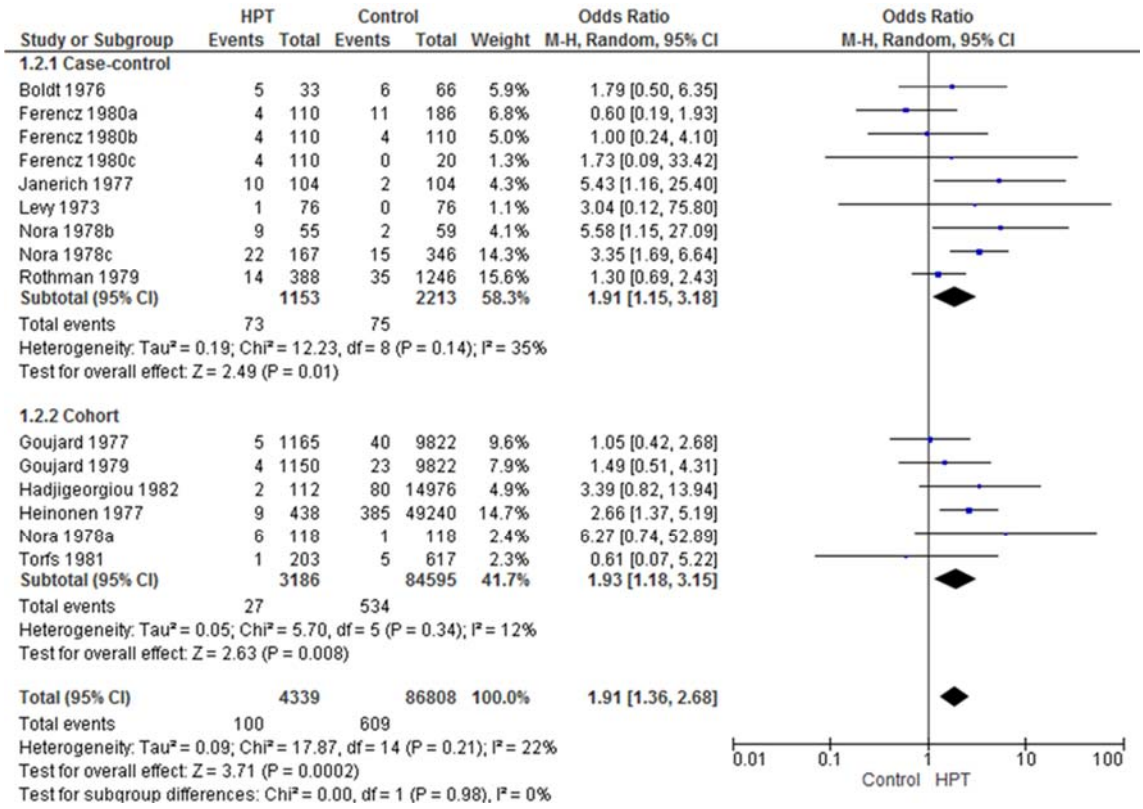
We were interested in analysing these data, because we had noted a footnote in Figure 2 of the original EWG report, a forest plot of data on heart defects, which stated that "weights are from random effects analysis", although neither weights nor pooled analyses were presented in the final report.

Having received the raw data that had been extracted by the EWG, we now present the results of a random-effects meta-analysis.

2. Results of meta-analysis of the data extracted by the EWG

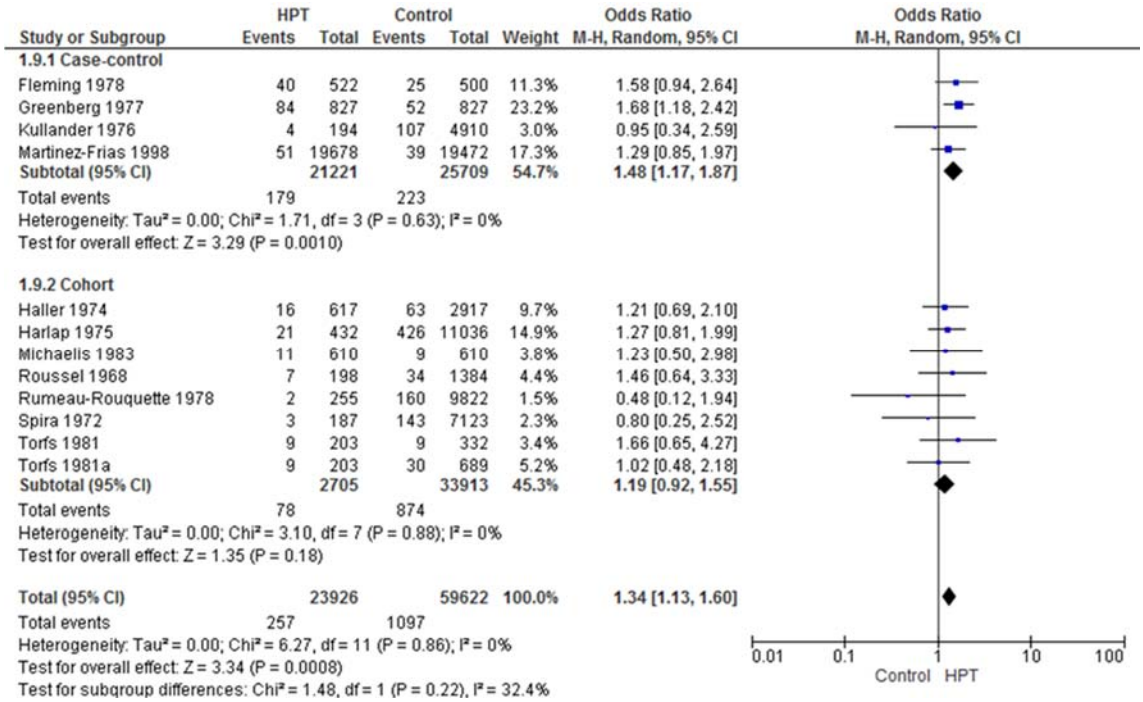
(a) Congenital heart defects

Analysis of the data presented in the EWG report shows a significant association of oral HPTs with a risk of congenital heart defects: OR = 1.92 (95% CI = 1.36 to 2.68; $I^2 = 22\%$; $P = 0.0002$; data from 9 case-control studies and 6 cohort studies).



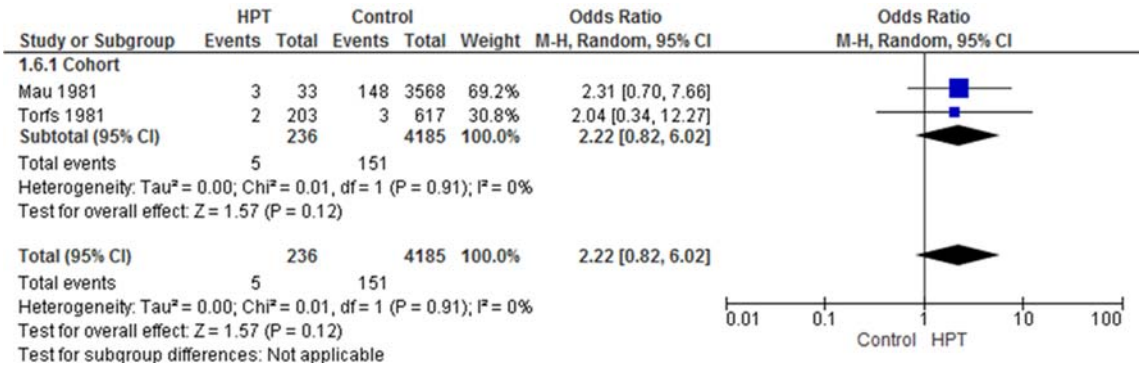
(b) Any congenital malformation

Analysis of the data presented in the EWG report shows a significant association of oral HPTs with a risk of any congenital malformation: OR = 1.34 (95% CI = 1.13 to 1.60; I^2 = 0%; P = 0.0008; data from 4 case-control studies and 8 cohort studies).



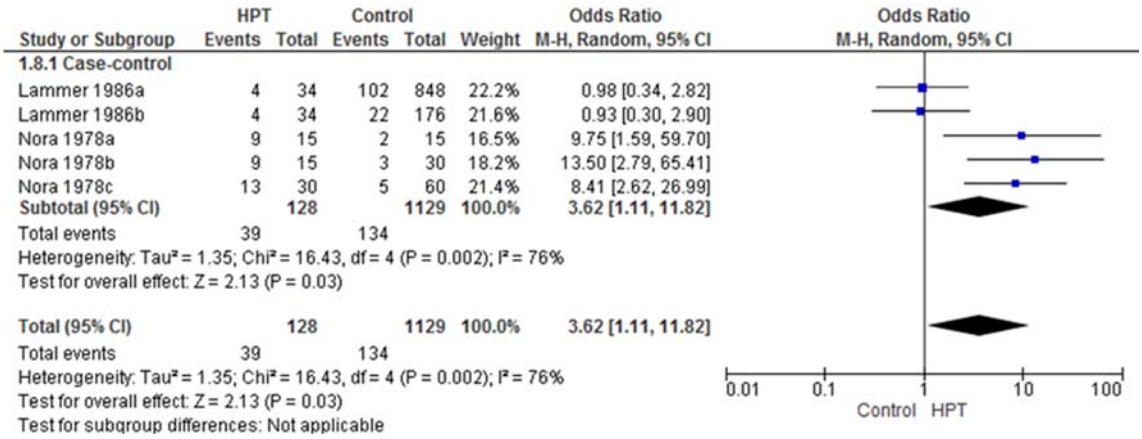
(c) Urogenital defects

Analysis of the data presented in the EWG report shows a non-significant association of oral HPTs with a risk of urogenital defects: OR = 2.22 (95% CI = 0.82 to 6.02; I^2 = 0%; P = 0.12; data from 2 cohort studies).



(d) "Other" defects

Analysis of the data presented in the EWG report shows a significant association for congenital "other defects"; OR = 3.62 (95% CI = 1.11 to 11.82; data from 5 case-control studies). However, significant heterogeneity (I^2 = 76%) across these 5 studies suggests that these results should not be combined; the term "other" probably reflects very different outcomes.



3. Conclusions

The results of meta-analysis of the data presented in the EWG review* [2] are similar to those found in the Heneghan et al systematic review [1]. Both reviews show significant associations of HPTs with all congenital malformations and congenital heart defects, and a non-significant association with urogenital defects.

The criteria for including studies differed between the two meta-analyses, as Heneghan et al focused the question solely on exposure to HPTs and excluded exposure to other hormones.

However, both systematic reviews show that the use of oral HPTs in pregnancy is associated with increased risks of congenital malformations (Table 2).

Table 2. A comparison of analyses of the data presented in the EWG report and those presented by Heneghan et al.

Malformations	**EWG results [2]**	**Heneghan et al results [1]**
Congenital heart defects	OR = 1.92 (95% CI = 1.36 to 2.68; I^2 = 22%; P = 0.0002)	OR = 1.89 (95% CI = 1.32 to 2.72; I^2 = 0%; P = 0.0006)
Any malformation: EWG: any congenital malformation Heneghan et al: all congenital malformations	OR = 1.34 (95% CI = 1.13 to 1.60; I^2 = 0%; P = 0.0008)	(OR) = 1.40 (95% CI = 1.18 to 1.66; P < 0.0001; I^2 = 0%).
Urogenital malformations: EWG: genital Heneghan et al: urogenital	OR = 2.22 (95% CI = 0.82 to 6.02; I^2 = 0%; P = 0.12)	OR = 2.63 (95% CI = 0.84 to 8.28; I^2 = 0%; P = 0.10)

* Although the EWG data reported the ORs with 95% CI estimates for outcomes involving three studies (Lammer 1986, Sainz 1987, and Tummler 2014), the raw data for the events rates in these studies were not reported in the paper. These studies were, therefore not included in the meta-analysis

- Lammer 1986: nervous system; orofacial clefts; digestive and abdominal wall; limb defects;
- Sainz 1987: nervous system;
- Tümmler 2014: nervous system; urinary system; limb defects.

Authors

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Conflicts of interest

CH is an advisor to the All-Party Parliamentary Group on Hormone Pregnancy Tests,and he has presented the results of the systematic review at the UK Houses of Parliament and The Independent Medicines and Medical Devices Safety Review. CH has received expenses and fees for his media work, including BBC Inside Health. He holds grant funding from the NIHR, the NIHR School of Primary Care Research Evidence Synthesis Working Group (project 390), The NIHR Oxford BRC, and the WHO. The CEBM jointly runs the EvidenceLive Conference with the BMJ and the Overdiagnosis Conference with some international partners; these are based on a non-profit model. CH is Editor in Chief of BMJ Evidence-Based Medicine and an NIHR senior Investigator

JKA has published many review articles and original papers in peer-reviewed journals on adverse drug reactions; he has edited textbooks, for which he has received royalties; he has been remunerated for acting as an expert witness in cases involving suspected adverse drug reactions; he has presented the results of the systematic review discussed above to members of the Bundestag; he is a member of the Centre for Evidence Based Medicine (see above).

The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Acknowledgements:

Igho Onakpoya provided input to this letter and analysed the data using RevMan.

Reference

[1] Heneghan C, Aronson JK, Spencer E, *et al.* Oral hormone pregnancy tests and the risks of congenital malformations: a systematic review and meta-analysis [version 2; peer review: 3 approved]. *F1000Research* 2019, 7:1725 (https://doi.org/10.12688/f1000research.16758.2)

[2] Report of the Commission on Human Medicines' Expert Working Group on Hormone Pregnancy Tests. GOV.UK. https://www.gov.uk/government/publications/report-of-the-commission-on-human-medicines-expert-working-group-on-hormone-pregnancy-tests (accessed March 2019).

Note:

Table 1 (confounding variables collected and notes on matching/ adjustments made) is linked to in the webpage and is available at

https://www.cebm.net/wp-content/uploads/2019/03/Table-1-Description-of-cohort-including-numbers.pdf

Received: 17/05/2019

Dear IMMDS review team

There have been several criticisms of our decision to perform a meta-analysis and that it was inappropriate.

We note that in evidence given to the IMMDS Review: ORAL HEARINGS - Monday 28 January 2019, Professor Stephen Evans set out a position based on a publication of which he was an author, asserting that you should only ever perform meta-analysis for randomized trials. SM sought clarification as to when the book was published.

The relevant text in the hearing is (09.37 onwards)

And I was … er … one of the authors of a publication that came out … er … three years ago, "Evidence synthesis and meta-analysis for drug safety", where we set out, we think, where are the considerations for including observational data. A lot of people think that you shouldn't ever do it – you should only do it for randomized trials. When you've got randomization it's always sensible to do meta-analysis, and some people treat meta-analysis of observational data as if it were randomized data, and they're very different. And … er … the argument that we had in *that* book was that there *are* circumstances where observational data *can* be meta-analysed, but you have to be exceedingly cautious in your interpretation…'

SM: Can I just clarify? The book that you have there – that was written before the Expert Working Group?

We have now obtained a hard copy of the book referred to [reference 1] and attach the relevant page 41, section 3.10 which sets out the conditions under which it is appropriate to perform a meta-analysis of observational studies.

> 'Meta-analysis of observational studies may be considered for one or more of the following purposes'
>
> 'to provide evidence of the effects of interventions that cannot be randomized, or of outcomes that are extremely unlikely to be studied in randomized trials (such as long-term rare outcomes); and/or
>
> to study the effect in patient groups not customarily studies in randomized trials (such as children, pregnant women and older patients).'

We, therefore, consider that the CIOMS 10 report (referred to at the meeting on the 28th January) justifies meta-analysis, and wanted to make the committee aware of the relevant text from the report.

We have also copied in the chair of the APPG for reference.

References

1. Evidence Synthesis and Meta-Analysis: Report of CIOMS Working Group X. Year of publication: 2016. The Council for International Organizations of Medical Sciences (CIOMS). https://cioms.ch/shop/product/evidence-synthesis-and-meta-analysis-report-of-cioms-working-group-x/

Note: attachment not included as relevant text included in email.

Received: 01/08/2019

I'm writing as we have tracked down a copy of the Gal 1972 paper, published in Advances in Teratology, Volume 5. (pdf attached)

We wanted to bring it to your attention as we have analysed the results excluding mothers over 35 years of age, those with acute infections, a history of previous malformed siblings, or a history of infertility, and those with other confounding factors.

Attachment: Analysis of Gal and Greenberg

University of Oxford
Centre for Evidence-Based Medicine
Nuffield Department of Primary Health Care Sciences

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01/08/2019

Dear IMMDS review team

On 18 March 2019, C Heneghan and JK Aronson reported on the findings of the Heneghan et al systematic review "Oral hormone pregnancy tests and the risks of congenital malformations: a systematic review and meta-analysis" [1] to a meeting of an ad hoc expert group convened by the Medicines and Healthcare products Regulatory Agency (MHRA) in London.

The ad hoc expert group raised concerns about the evidence provided by Gal [2], as follows:

"In a separate publication Gal states that in 18 (of the 19 mothers) exposed to HPTs, who had malformed babies and were included in that study, pregnancy was unwanted (Gal et al., 1972 b). [2] This raises the question of whether the women using HPTs had underlying complications that meant they were different in some way that may make them more predisposed to having infants with congenital defects and questions the robustness of the study finding for an increased risk of neural tube defects (NTDs) with HPTs."

We tracked down a copy of the Gal 1972 paper, published in *Advances in Teratology,* Volume 5, which provides more detailed data on the material referred to briefly in the 1967 paper. [3] In the 1967 paper differences were found in the number of previous malformed siblings and the numbers of women with a history of infertility in the two groups. These cases were excluded in the Gal 1972 analysis, to eliminate bias that could have arisen by including women with a previous genetically malformed baby or other confounding factors.

Figure 1 shows the 95% confidence intervals (CI) of the results of excluding mothers over 35 years of age, those with acute infections, a history of previous malformed siblings, or a history of infertility, and those with other confounding factors. These exclusions do not remove the significance of the association. Figure 2 shows the 99% CI for these effects, providing more precision around the estimates.

Data from the Greenberg study are included in the figures, as it was the only other study we found that analysed data after removing mothers with underlying confounders. [4]

Ferencz (1980) assessed maternal hormone therapy and congenital heart disease. [5] They use multiple regression analysis controlling for confounding variables and created scores based on reproductive, malformation and exposure risk. This analysis showed no increase in relative risk for cases compared with matched controls.

Figure 1

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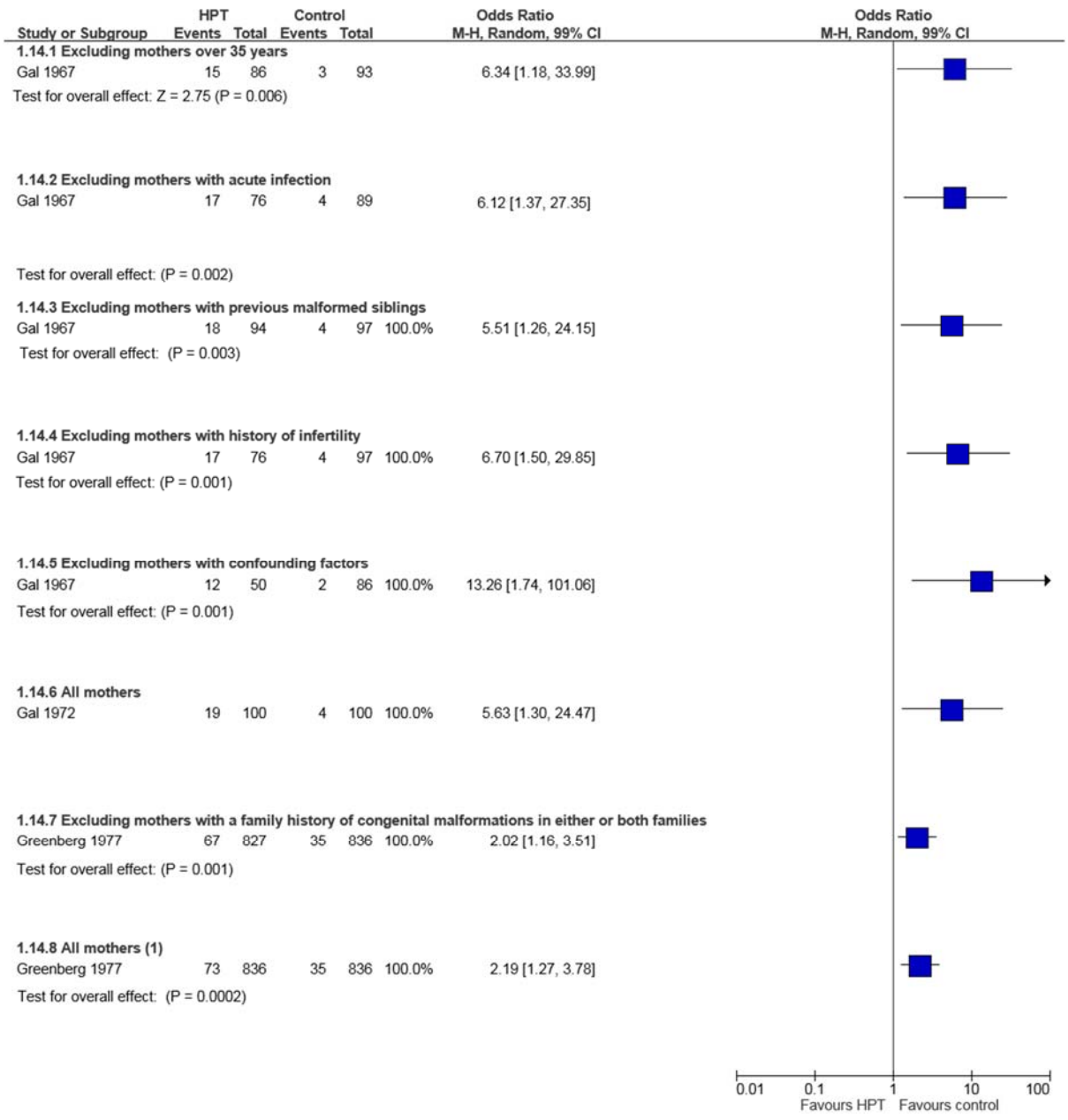
Centre for Evidence-Based Medicine
Nuffield Department of Primary Health Care Sciences



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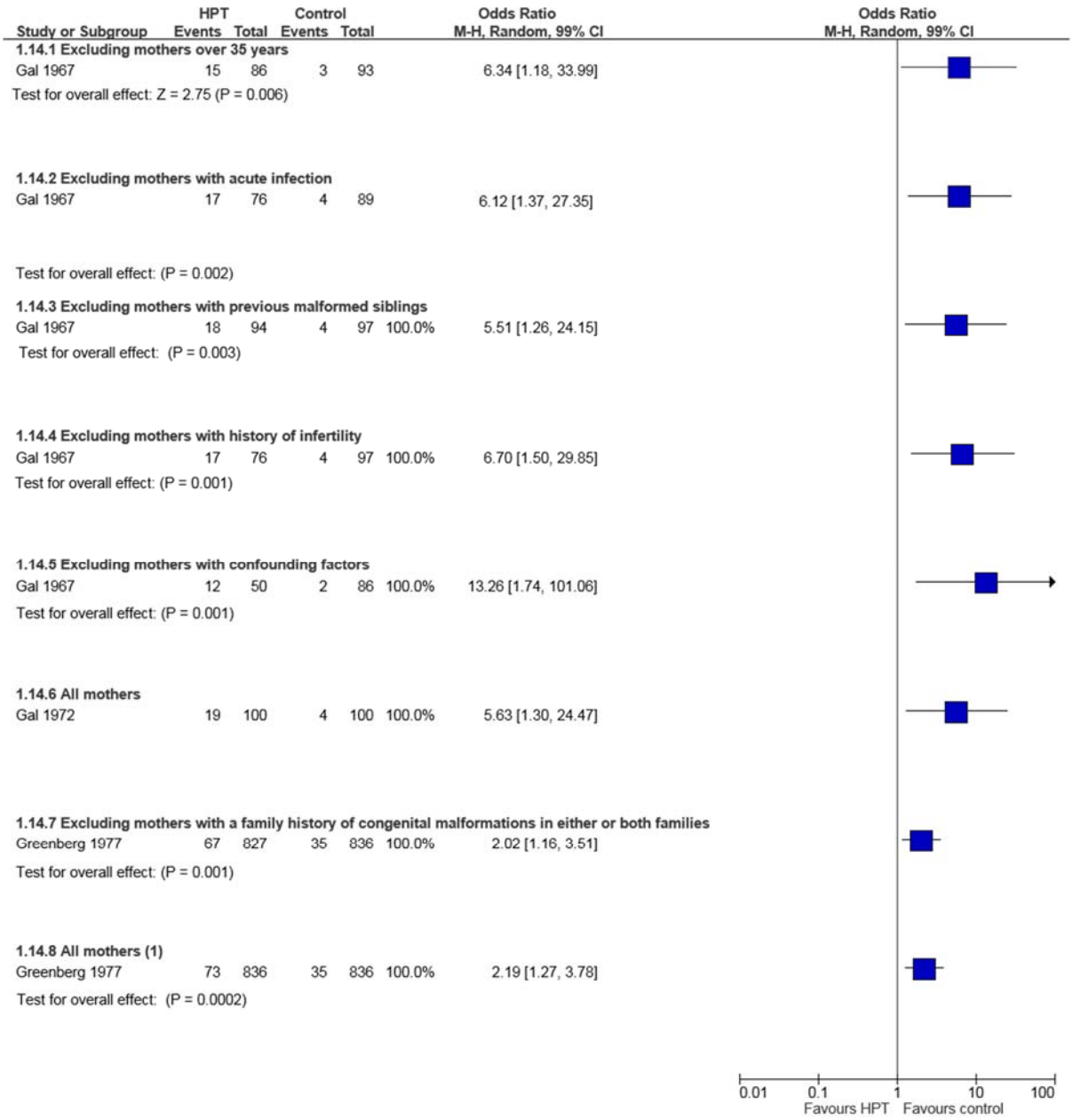
Nuffield Department of Primary Health Care Sciences

Figure 2



Carl Heneghan, Jeffrey K Aronson

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Competing interests: CH holds grant funding from the NIHR School of Primary Care Research Evidence Synthesis Working Group [project 390] and the NIHR Oxford BRC. He is Editor-in-Chief of BMJ Evidence-Based Medicine and an NIHR Senior Investigator. He is Director of the Centre for Evidence-Based Medicine (CEBM), which jointly runs the EvidenceLive Conference with the BMJ and the Overdiagnosis Conference with some international partners, which are based on a non-profit model. JKA has written and edited articles and textbooks on adverse drug reactions, including Meyler's Side Effects of Drugs (16th edition, 2016), its companion volumes the Side Effects of Drugs Annuals, and Stephens' Detection and Evaluation of Adverse Drug Reactions (6th edition, 2011). He is an Associate Editor of BMJ Evidence-Based Medicine and a member of the CEBM (see above).

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Dr Wael Agur

Subspecialist and Lead Urogynaecologist | NHS Ayrshire & Arran Honorary Senior Clinical Lecturer | University of Glasgow | Scotland

Dr Agur shared the following documents with the Review:

- Ong, H.L., Sokolova, I., Bekarma, H. et al. (2019) Development, validation and initial evaluation of patient-decision aid (SUI-PDA©) for women considering stress urinary incontinence surgery. International Urogynecology Journal doi: 10.1007/s00192-019-04047-z
- Stress Urinary Incontinence – Patient Decision Aid (SUI-PDA©). NHS Ayrshire & Arran. https://www.nhsaaa.net/media/7598/mis17-214-gd-stress-incontinence-form.pdf
- Views of the Scottish Mesh Survivors Group on the Service provided to the Mesh-injured Women in Scotland. Presented to The Scottish Government Accountable Officers Short-Life Working Group on Friday 14th June 2019. This is available on the Scottish Mesh Survivors website: http://www.scottishmeshsurvivors.com/pdf/SBAR_SMS_for_Publication_230619.pdf
- Management of Pelvic Mesh Complications in Scotland. Preliminary Results of a Service Evaluation co-designed by Patients and Clinicians. https://www.parliament.scot/S5_PublicPetitionsCommittee/Submissions%202019/PE1517_HHHH_Comb.pdf

Dr Rebecca Bromley

Research Fellow & Clinical Psychologist, University of Manchester

Shared a letter (on following page) and article which updates on the information previously provided by: Professor Jill Clayton-Smith, Dr Rebecca Bromley, Professor Peter Turnpenny, Professor Amanda G Wood.

- Jill Clayton-Smith, et al. (2019) 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 14: 180 doi:10.1186/s13023-019-1064-y

The University of Manchester

Dr Rebecca Bromley, ClinPsyD, PhD

Research Fellow & Clinical Psychologist

The University of Manchester,

St Mary's Hospital, Manchester

Dear IMMDSR Team,

Thank you for requesting a copy of our diagnosis framework paper, a copy is attached.

I also wished to use this opportunity to update you on an exciting new development in that we are now in the process of establishing a dedicated Fetal Valproate Spectrum Disorder clinic at Royal Manchester Children's Hospital. This will be a collaboration between Genetics (Prof Clayton-Smith) and Neuropsychological (myself). We have done this informally on an adhoc basis for a number of years, but finally I will have dedicated time for this work (2 days per week). We are likely to be accepting referrals from late Spring 2020. The provision is limited, but it is a step in the right direction. I know that Dr Turnpenny also aims to establish a similar clinic in Exeter and we will work together to ensure that the two services mirror each other and allow us to learn more about the condition. However, a Department of Health funded network of multidisciplinary clinics remains the goal in the longer term.

I also wanted to mention a couple of things which have come to mind whilst I have been watching the oral testimonies. The neurodevelopmental difficulties associated with fetal valproate exposure took such a long time to uncover and this is for a number of reasons:

1) No one was looking. Teratology centres and research groups were established in the wake of the thalidomide situation. Due to this drug being a strong physical teratogen, affecting numerous bodily systems, the area filled with geneticists and expertise on the physical development of the foetus. Thus there were few who were invested or had the expertise to look at the cognitive, social or behavioural developmental side. Whilst this is changing we still see the child's physical outcomes taking centre stage in teratology research, funding, conference presentations, papers and chapters.

2) Neurodevelopmental outcomes are not immediately obvious. Major congenital malformations are of course easier to collect data on and there are numerous national and international systems through which birth defects are monitored. However, there is no such system in place for neurodevelopmental outcomes. GPs are unlikely to ask about the child's cognitive abilities (unless very severe or a problem spontaneously reported by the family) and therefore health professionals may be unaware of a cognitive difficulty and therefore this does not get reported through the Yellow Card Scheme (or other national spontaneous reporting systems). The exception to this are the autism spectrum disorders which are diagnosed through the NHS; although those cases with a diagnosis are often only the tip of the iceberg.

3) Neurodevelopment is a broad term which covers a whole host of different skills, which are unlikely to be uniformly affected by a teratogen (different brain tissue subtypes will respond to the teratogen differently). Thus, looking in one area (i.e. autistic spectrum disorders) is not going to provide the answer for all aspects of brain functioning. IQ and other cognitive skills are assessed by specialists and such assessments are not undertaken routinely anywhere in the world and therefore this data is hard to amass, unless there is a specific, targeted investigation. We do, of course, have educational outcomes which are routinely collected, but please refer to my comment below.

4) The seriousness of the neurodevelopmental outcomes were not taken seriously. Sadly, when I first started looking into the cognitive outcomes of children exposed to anti epileptic drugs there were a lot of negative comments made to me about the significance of the impact on the developing brain from some neurologists and pharmaceutical representatives. Some also held the belief that because certain epilepsy types carry a cognitive risk, that the children had 'inherited' poorer cognitive skills from the mother. Whilst a small number of children may present with cognitive difficulties which are linked to a gene known to be associated learning disability (and in some cases epilepsy also) this is a small number and does not account for the pattern seen across populations exposed to valproate. It is my personal belief that it took regulatory action for the vast majority of neurologists to truly accept the link between fetal valproate exposure and child neurodevelopmental outcome (even those who had stopped prescribing valproate routinely). For this reason we need a more expedient pharmacovigilance system where neurodevelopmental outcome is central.

A number of testimonies mentioned using new methodologies to speed up data collection and on at least two occasions using educational records as a proxy for brain functioning was suggested. This is certainly something which requires exploration, and we have seen over the last two years that the impact of valproate would be detected using these research techniques. However, such 'routine data' or 'population data' have limitations; particularly with regards to information on confounding variables and the sensitivity of the measurement. Epidemiology methods which use ‘routinely collected’ health and education data are limited in their ability to provide information on key confounders such as maternal IQ, alcohol and nicotine in many cases. Further, examinations are a proxy for brain functioning and not a direct as educational skills are learnt behaviours rather than innate skills and numerous other influencers alter our educational performance. Further, there would be a significant time lag between the onset of a medications use and adequate numbers of exposed children reaching SATs or GCSE age when this data could be collected. We currently have a project underway to investigate the application of ‘population’ and ‘routine data’ sources as part of the CONCEPTION study (see below). It would be my hypothesis that these studies would be good tools for a 'first look' but then would require further investigation using direct studies and are likely only to detect the most severe neurodevelopmental teratogens.

I notice that the issue of funding was raised with you in a number of oral testimonies. I cannot highlight enough the impact a lack of funding has on progress. There are too few of us researching this topic and there is too little finance available. We have had the majority of our research funding from Epilepsy Research UK and the US National Institute for Health to date. To my knowledge none of the major UK research councils have funded anything in this area (medicine exposure and child outcomes). Frequently we apply to the Medical Research Council, with varying projects and despite very good reviews and excellent comments on the impact this would have on families and prescribing, we are yet to obtain funding. This is of course, academic life. However, when we are going up against diseases with large interest such as alzheimer's, getting studies which look at medical harms in a relatively small percentage of the population is difficult; even with a highly peer rated proposal.

I am please to inform you however that there is a positive piece of news on the funding front. I am involved in a five year project called *‘Building a pan-European ecosystem for generating, monitoring, and providing robust information on medication safety in pregnancy and breastfeeding’* the concePTION study. This is a very large consortium of researchers, pharmaceutical companies and regulators. The overarching aim is to re-develop pharmacovigilance for medication use in pregnancy. There are numerous aspects to this work that range from developing swine models for breast milk testing through to improving data collection directly from pregnant patients and their children. This is being led by the University Ultrech and the press release can be found here: https://www.prnewswire.com/news-releases/conception-building-a-pan-european-ecosystem-for-generating-monitoring-and-providing-robust-information-on-medication-safety-in-pregnancy-and-breastfeeding-300867205.html. We expect that this project will make a number of recommendations with regards to post market surveillance for products used in pregnancy. Currently, it takes on average

27 years to determine teratogneic risk or safety [1] and whilst this project will have a large impact on this, there will remain a tremendous amount of work to be done when this project ends; particularly with regards to implementing the recommendations and new systems.

Thank you for taking the time to read the above. Please let me know if I can be of any further assistance. I look forward to the conclusions of your review.

Best wishes,
Rebecca

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Dr Jonathan Sher

Deputy Director, Queen's Nursing Institute Scotland. Formerly Visiting Expert at Edinburgh University's Scottish Collaboration for Public Health Research and Policy

Provided the following article, reproduced here with the kind permission of the International Journal of Birth and Parent Education.

- Sher (2018) Taking valproate during pregnancy is a serious risk: An update on practice implications. International Journal of Birth and Parent Education. 5(3): 11-14

Taking valproate during pregnancy is a serious risk: An update on practice implications

Jonathan Sher
Independent Consultant and Visiting Expert at Edinburgh University's Scottish Collaboration for Public Health Research and Policy (SCPHRP)

The risks of inadequate warnings about damage done by valproate exposure in utero have become a focus of national and international attention by policymakers (Hunt, 2018; European Medicines Agency [EMA], 2017). There is a pressing need now for a 'new valproate prevention programme' in the UK and in Europe. This includes assessing pregnancy potential/intentions, pregnancy tests before and during treatment with valproate, individualised counselling, informed consent using a new 'risk acknowledgement form', regular reviews of treatment, and effective contraception while taking valproate. Crucially, there is now equal emphasis on all women of childbearing potential, replacing the previous focus on already pregnant women. Strengthening preconception education about valproate is a welcome preventative development.
Keywords: preconception, women's health, teratogens, valproate, European Medicines Agency, birth defects, pregnancy

Two years ago, when I cited the prescription medication 'valproate' as an example of the need for preconception education, counselling and care, there was little reaction (Sher, 2016). Now, a tipping point has finally been reached. Why? Not because of a recent scientific breakthrough or dramatic new research findings.

Valproate is a powerful teratogen (i.e. something capable of harming normal fetal development). This was established by decades of rigorous undisputed evidence (Meador & Loring, 2016; EMA, 2014; Meador et al, 2013). Among live births, up to 40% of babies exposed to valproate in utero experience long-term neurodevelopmental problems, while 10% are born with significant physical abnormalities (Meador, 2016; Medicines & Healthcare products Regulatory Agency [MHRA}, 2016). Valproate exposure can also cause miscarriages and stillbirths.

> Valproate is not a rare medication. In England alone, approximately 23,000 prescriptions are given to girls and women of childbearing age every three months (NHS England, 2017; NHS Digital, 2015).

The impetus for current attention and action did not come from health professionals. Instead, it is primarily the families whose children (now often teens or adults) suffered lasting impairment who prompted this 'discovery' of valproate. They are angered by inadequate warnings, as well as the lack of preconception advice and consent. They are also very discontent about the paucity of follow-up treatment and the absence of compensation from manufacturers, prescribers or government (EMA, 2017a; Martin, 2017). Historical, and ongoing, shortcomings led valproate victims to band together to enlist both policy and legal advocates. As is often the case, it has taken campaigners years of perseverance to become an 'overnight success'. By means of legal action and protests, the families pressured national agencies to pay attention. There has been direct action in the UK to gain support from the families' Westminster representatives. Major lawsuits have been filed in France and France's parliament has established an initial compensation fund for valproate victims (Health News, 2016, www.reuters.com/). The French medicines regulator (ANSM) had already taken independent action and then pressed the EMA to consider more robust regulations and warnings about the avoidable negative outcomes of this teratogen (ANSM, 2017).

The formidable European Medicines Agency never held a Public Hearing during its 22-year history – until last year. EMA's first-ever Public Hearing occurred in September 2017. The single subject was valproate (EMA, 2017b). The Hearing was fascinating, occasionally heart-rending and remarkable for more than being a first. Many individuals (mostly women) shared their lived experiences and specialist organisations provided supporting evidence. A remarkable feature was the oft-expressed desire for EMA not only to create more effective warnings but also to go well beyond this and recommend broader actions. This reflected the concern that stronger warnings - and even quality informational materials, e.g. the UK's 'Valproate Toolkit' - might not be adequate in preventing continuing harm (MHRA, 2016a). Making informational materials available does not guarantee they will be read, understood and change behaviour among patients, prescribers, dispensers and distributors. The final noteworthy aspect of this Public Hearing was its heavy emphasis on epilepsy. Valproate was originally

created as, and remains, an effective epilepsy medication. A small proportion of women will still require it to prevent severe seizures, even during pregnancy. It was agreed, however, that valproate should only be used during pregnancy when no effective alternative exists.

Valproate's high teratogenicity is why women with epilepsy have historically been most likely to receive preconception counselling, monitoring and care. 'Most likely' does not mean universally, as repeatedly pointed out to the EMA. Crucially, however, the reality is that valproate has been prescribed, dispensed and taken by many women of childbearing potential for numerous reasons other than epilepsy – such as migraine prevention, personality disorders and mood swings, pain relief, aggression and bipolar disorder (Murphy et al., 2016; Adedinsewo et al., 2013).

Pre-prescribing counselling of women and girls about the dangers of valproate appears inadequate

The EMA's Public Hearing focussed heavily on epilepsy, but only lightly on these other uses, including the 'off label' ones. No explicit attention was paid to the efficacy of 'off label' prescribing of valproate to girls and women of reproductive potential. This is particularly worrisome, given that there are alternative medications - possibly equally effective and less teratogenic - available for all the conditions for which valproate is currently prescribed (Wen et al., 2015). There was a corresponding lack of information at the Public Hearing about any efforts made to warn about, or prevent, prescribing valproate to girls and women of childbearing potential who do not have epilepsy. No evidence was offered that these women routinely receive adequate preconception care, monitoring and counselling. In fact, one alarming, small-scale survey in England reported that: 'The use of valproate [2005-2012] was increased overall by 64% and there was an 18% increase in off-label valproate use. The rate of clinical discussion carried out during commencement declined from 70% to 35% and at annual review from 50% to 22%' (Atturu & Odelola, 2015).

In the absence of a serious informed consent process, no competent physician would prescribe valproate to a woman known to be pregnant. However, in the UK and some other Organisation for Economic Co-operation and Development (OECD) nations, roughly half of all pregnancies are still unplanned, unintended or mistimed. Thus, women sometimes continue taking valproate before knowing they are pregnant and so, inadvertently risk avoidable harm. Preconception action is especially important since, as was pointed out during the EMA's Public Hearing, it is not safe to discontinue or replace valproate immediately. At least one month's weaning is recommended.

Early this year, the EMA, which will move its headquarters from London, post-Brexit, issued its findings (EMA, 2018) and recommendations based upon the Public Hearing and other submissions to its Pharmacovigilance Risk Assessment Committee (PRAC). This brief document is well worth reading. The EMA's encouragement of new restrictions is a major step forward in several respects. It states that valproate 'must not be used' in pregnancy, with rare exceptions for individual women: a) having epilepsy and b) for whom there is no effective alternative medication. The EMA calls for stronger, more ubiquitous warnings, patient reminder cards and updated educational materials.

Equally important, it underscores the pressing need for a 'new valproate prevention programme'. This includes assessing pregnancy potential/intentions, pregnancy tests before and during treatment with valproate, individualised counselling, informed consent using a new 'risk acknowledgement form', regular reviews of treatment and effective contraception while taking valproate. Crucially, there is now equal emphasis on all women of childbearing potential, replacing the previous focus on already pregnant women.

There is an urgent need for a valproate prevention programme

Strengthening valproate's preconception, preventative element is a welcome development. Whether these European recommendations will be implemented in the UK is yet another post-Brexit mystery. The signs are positive. A senior official within the UK's MHRA chairs the PRAC at present. In February 2018, following media attention and pressure upon Westminster politicians, the Prime Minister and the UK's Health Secretary announced a major review of valproate. As it is not in the EMA's remit, there was no action recommended about the treatment of, or compensation for, past valproate victims. This presents a continuing challenge for campaigners in both the UK and Europe.

One oft-forgotten impediment to avoiding valproate harm is confusion about the name.

People are becoming increasingly familiar with valproate as a medication to be avoided if pregnant, of if trying/likely to conceive. But, very few women of childbearing age are given a generic prescription for 'valproate' or 'valproic acid'. Instead, women in Europe/UK read on the box or label that they are taking: Absenor, Convival Chrono, Convulex, Delepsine, Depakin, Depakine, Depakote, Depamag, Depamide, Deprakine, Diplexil, Dipromal, Epilim, Episenta, Epival, Ergenyl, Espa-Valept, Hexaquin, Kentlim, Leptilan, Micropakine L.P., Orfiril, Petilin, Valepil, Valhel PR, Valpal, Valpro or Valprolek. This disconnects the active ingredient from the brand name, which can easily contribute to confusion and unintentional risk-taking.

WHAT SHOULD BE DONE ABOUT TERATOGENIC AGENTS OTHER THAN VALPROATE?

Of course, valproate is not the only teratogenic medication prescribed in the UK, Europe or worldwide (Bastow et al., 2017). Will the EMA limit itself to this one medication or is this the beginning of an effort by national and international regulatory agencies to deal better with all drugs known to create risks for adverse pregnancy and birth outcomes?

As health professionals know, but many in the general public do not, teratogens exist in very different forms. They can be environmental, e.g. radiation or hazardous chemicals in the workplace, neighbourhood or home; or, communicable diseases, e.g. rubella or zika virus, as well as medications and other consumable products.

Teratogens of any kind jeopardise what anyone intending to become a mother or father deeply desires: a safe pregnancy, a thriving baby and rewarding parenthood. Sadly, these positive outcomes are far too often not achieved, while the harm is inequitably distributed (Sher, 2016a). While beyond the remit of the EMA, alcohol remains one of the most common and potentially most potent teratogens. Across the UK, in particular, there is a continuing 'blind spot' about preventing or identifying Fetal Alcohol Spectrum Disorder (FASD), or properly supporting those already affected (May et al., 2018; British Medical Association, 2017; de Caestecker & Sher, 2017; Jonsson et al., 2014).

Neither 'crying wolf' nor 'burying one's head in the sand' is helpful in preventing the risks of valproate or any other teratogen. Both extremes are counterproductive for prospective mothers and fathers. What they want and need is respectful support to make genuinely informed, empowering choices about preparing for pregnancy and parenthood.

Dr Jonathan Sher can be reached at:
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Best practice guidelines for warning about the risks of all proven teratogens

When discussing the risks of proven teratogens in pregnancy, advice given should be:

Respectful and compassionate
Toward every individual being cautioned about established risks. Naming, shaming and blaming people when their behaviours (often inadvertently) undermine their good intentions is both cruel and ineffective.

Proportionate to the proven risks
Warnings and other primary prevention activities should have at their core information that is accurate, easily understood and, most importantly, explains clearly why the advice being given is worth heeding.

Given and received early
And shared widely enough to reach all relevant people (especially those of reproductive potential) to allow sufficient time for necessary changes and primary prevention to occur. The means getting the right information at the right time to the right people instead of, for instance, waiting until the 'first booking appointment' when a pregnancy is already underway. Prescribers of teratogenic medications have a responsibility to provide the information and counselling necessary for there to be meaningful informed consent before the first prescription is written for any girl or woman of reproductive potential.

Accompanied by assistance
There should be easy access to opportunities to receive the help needed to make necessary life-style changes, including switching medications. In addition, valproate and some other medications can supress folate levels, which means increased Vitamin B9 (folic acid) supplementation should be routinely encouraged before and early in pregnancy (Meador, 2018). Public health campaigns should be combined with relationship-based preconception and antenatal counselling. While well-constructed, broadly distributed, key messages are helpful in raising societal awareness and cultural sensitivity, they are not enough by themselves. People are persuaded by, and act upon, personalised information and advice from trusted, respected sources (Sher, 2017; Allen et al., 2012; Nolan, 2009).

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Professor Charles Vincent

Experimental Psychology, University of Oxford

Provided the following paper:

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Questions of May 2019 from the Independent Medicines and Medical Devices Safety Review to Bayer plc and Bayer's answers

Written Questions

1. Concerns over Primodos have been ongoing for half a century, you now have this review as well as a review in Germany. It would be in everyone's interests that this is resolved, how do you see this happening?

Answer

It was only in 2009 that Bayer first became engaged in issues surrounding the marketing of Primodos in the UK. In that year, as you are probably aware, Mr [redacted], approached Bayer and sought compensation. His claim was rejected by Bayer plc, but in May 2011, [redacted], solicitors for a group of claimants, including Mr [redacted], notified Bayer plc that the Legal Services Commission had granted some funding to enable these solicitors to review the history of the claims and the medical and scientific literature and to advise whether there was any new evidence since 1982 bearing on causation. Bayer was asked to provide its view on this question and the scientific literature that had been considered so that it could be considered with the expert(s) that this solicitors' firm intended to consult on the scientific issues.

Following further correspondence, on November 2011 Bayer provided its analysis of the post-1982 literature to both [redacted] and the Legal Services Commission. It believed that, far from evidencing a scientific revolution on the subject, the post-1982 literature, in fact, hardened the evidence against the existence of a causal relationship. This view was supported by an external expert, Professor Michael Bracken who was Professor of Epidemiology, Obstetrics and Gynaecology, Reproductive Science and Neurology at Yale University who considered that the available evidence (in November 2011) did not point to female sex hormones used by a mother during pregnancy increasing the chance of her offspring being congenitally malformed. Bayer's review also noted that in 1987 the FDA in the US held a hearing in which the FDA, the Teratology Society, the Centers for Disease Control and Prevention and the American College of Obstetrics and Gynaecology supported the conclusion that progestational agents do not result in non-genital malformations. The FDA allowed a cautionary warning previously included in the product information for such products to be removed. Individual researchers had reached the same conclusion. In his 2005 review, the eminent American teratogist, Robert Brent, Professor of Pediatrics at Jefferson Medical College of Thomas Jefferson University and a fellow of Fitzwilliam College, Cambridge, reviewed the history of the FDA warning and its removal and concluded that the allegation that exposure of pregnant women to sex steroids led to an increased risk of non-genital congenital malformations in their offspring was erroneous.

Thereafter, Bayer heard nothing further from [redacted] and no claims were served. However, Mr [redacted] continued to correspond with Bayer and in May 2013 a Pre-Action Protocol Letter of Claim was received from new solicitors, [redacted], seemingly acting for Mr [redacted] alone under a conditional fee agreement. It alleged negligence and sought damages provisionally assessed at £1.3m. Following Bayer's response no proceedings were actually served upon Bayer.

You are already aware of the EWG Report and the deliberations of the European Medicines Agency on two referrals by the UK relating to particular scientific publications. We are not aware of any further scientific review planned by the regulatory authorities in Germany or elsewhere.

The conclusions of the review of the claimants own legal team in 1982 and the conclusions of all the reviews to date by independent regulatory authorities are consistent in finding that there is no causal connection between exposure to sex hormones in pregnancy, or Primodos in particular, and a higher incidence of congenital malformations.

Evidence

2. We have seen the evidence considered by the Expert Working Group, including evidence from the Berlin LandesArchiv. Are you aware of:
   a. Any relevant information in Bayer's possession that was not disclosed in the litigation in the early 1980s
   b. Any relevant information that was not considered by the EWG?
   c. Any tests carried out by Schering that are not listed in the Landesarchiv and available on the MHRA website (https://mhra.filecamp.com/public/files/2rbs-ceca8bra)?

Answer

Both Schering AG and its subsidiary Schering Chemicals Ltd were defendants in the litigation that began in 1978 and ended in 1982 and as such made disclosure of all documents then in existence relevant to the issues in the action relating to both the history of marketing of Primodos in the UK and the question of whether hormone pregnancy tests were capable of causing congenital abnormalities in the newborn. Marketing of Primodos in the UK ended in 1978. Scientific information and opinion and research results that came into existence after 1982 would obviously not have been part of this litigation.

Bayer provided the MHRA with details of all known Schering research data relevant to Primodos and the active substances upon which it was based, but Bayer has not 'audited' the LandesArchiv to check which studies were also included in that archive. The documents in this Archiv were collected well before the discontinuation of the English litigation and Bayer does not understand them to represent a complete picture of available research data, as provided to the MHRA.

As noted above in our answer to Question 1, Bayer undertook a review in 2011 of whether any new data had become available after 1982 that might amount to a material change in scientific knowledge in this area. It concluded that there were no new data that put in doubt the conclusions reached in 1982 on the issue of causation and which caused the claimants legal team to advise discontinuation of the proceedings. Bayer's 2011 review of post-1982 epidemiological literature and opinion was made available to the MHRA.

Accordingly, we are not aware of any relevant scientific research data held by Bayer from the old Schering files or Bayer's review of data published between 1982 and 2011 that were not made available to the MHRA. The EWG's report indicates what data they considered and treated as relevant.

Bayer provided details of all scientific data available to it relating to the issue of causation including all animal tests and trial information in its possession. Bayer is not aware of any other tests or trials carried out by Schering or Bayer that are relevant to the issue of causation.

Product development

3. The 1950s were a different culture. There are mentions in the Landesarchiv documents that Primodos was developed as an emergency contraception, or an abortive. Could you tell us:
   a. What was it initially meant to be?

b. How did end up being used as a pregnancy test?
c. What pre-market tests were done?

Answer

It is over 60 years since Primodos (Duogynon oral) was developed as a medicinal product by Schering AG. Such of the contemporary documents relating to this period as exist show that it was developed as a pregnancy test and for the treatment of secondary amenorrhea not due to pregnancy. It should be borne in mind that oestrogen-progesterone products, either in combination or alone, had been used since the early 1930s for treating various types of amenorrhea and for treatment of patients prone to miscarriage (so called hormone support therapy). Schering marketed injectable preparations for pregnancy testing and treatment of amenorrhea (but not in the UK) and only later developed oral forms in 1950s. Therefore, Primodos was not a novel concept, but rather a more convenient form of an existing product. The suggestion that the product might have been developed as an emergency contraceptive or as an abortifacient would be counter-intuitive given that related hormones were used as hormone support therapy to avoid miscarriage.

Trial information collated by Schering in 1981 for the purposes of the litigation was made available to the MHRA. It appears that before 1958 there were 27 published studies with injectable preparations and 11 with oral preparations. Over 700 patients received combined oestrogen-progestogen preparations of which 160 were for pregnancy diagnosis. Between 1958 and 1971 there were published a further 13 studies with oral preparations and this included 295 patients for pregnancy diagnosis and 862 cases for menstrual disorders. These studies reported the hormone preparations in question to be accurate in diagnosis and efficacious in the treatment of various types of amenorrhea and to have a positive benefit to risk balance.

These studies refer to the concept of treatment with oestrogen-progestogen combinations and not just Primodos/Duogynon oral, because manufacturers of hormone pregnancy tests used different combinations of oestrogens and progestogens. The trial documents provided to the MHRA included a translation of an internal document of 1958 in German of Schering AG's Clinical Research Group that referred to the development and registration of Primodos/Duogynon oral as being for the treatment of secondary amenorrhea and for use as a pregnancy test and describes where trials had been conducted. There is no suggestion of development for emergency contraception or as an abortifacient. Indeed, it is stated that a "damaging influence on pregnancy is not possible since progestogens as well as oestrogens support the maintenance and development of a pregnancy".

Bayer also made available to the MHRA all the Schering animal studies performed at any time on norethisterone acetate and ethinyl oestradiol and the combination in all doses and in all animals, including primates. These studies are described in detail in the EWG Report which concludes that they do not present evidence of teratogenicity.

4. What was the benefit profile of Primodos?

Answer

Until 1970, Primodos was recommended as a pregnancy test and for the treatment of secondary amenorrhea not due to pregnancy. When Primodos was introduced in the UK as a pregnancy test in 1958 literature indicates that it was viewed, as with the many other hormone pregnancy tests available in the UK from different manufacturers, as of comparable reliability to biological tests such as the Xenopus Toad test, but capable of diagnosing pregnancy immediately after the first menstrual period has been missed, whereas biological tests required a wait before chorionic gonadotrophin appears in the

urine of the patient. It was also simple for administration and instruction to the patient and prescribable on a NHS prescription. Published promotion at the time noted that it was considerably cheaper than a biological test and saved the patient the inconvenience of collecting and posting a urine sample.

From 1970, Primodos and products like it were recommended in the UK only for treatment of secondary amenorrhea of short duration (less than one year) not due to pregnancy and the treatment could normalise ovarian function so that spontaneous cyclical bleedings would follow. The independent clinical commentary in the British National Formulary of 1974-76 continued to note that oestrogen/progesterone combinations were frequently used for menstrual disorders.

5. What proportion of Primodos use was for pregnancy testing and what proportion for secondary amenorrhea in the UK? How did this change over time?

Answer

This issue was discussed with the MHRA in the context of a report from the early 1980s by the then medical director of Schering Chemicals Ltd, Dr R.A. Wiseman, which appears at Annex 13 in the EWG Report. The report included sales figures for certain HPTs, but did not include any data on differential use. Bayer pointed out that the only historic document on this subject, available to Bayer, was one from 1966 which quotes (based on some form of sampling in all probability by an outside agency called 'BMI') that 75% of Primodos prescriptions at that time was for pregnancy diagnosis and 70% of Roussel's equivalent product (Amenorone Forte) was for pregnancy diagnosis. In each case the balance would have been for regulation of menstruation. This is a much higher use as a pregnancy test than had been estimated by Dr Gal whose figures are referred to in the EWG Report. Between 1968 and 1975 she said the figure for use as a pregnancy test was no higher than 19.4% for HPTs generally. This seems counter-intuitive, at least up until 1970, given the common name given to such products (hormone pregnancy tests). However, Dr Wiseman notes in his report, when he considers the likely number of women who were pregnant when using HPTs (p12), that it is reasonable to assume that a variation in the percentage of women receiving HPTs who were likely pregnant and not pregnant would have occurred after 1970 when the indication of pregnancy testing was deleted by all manufacturers and again in 1975 after the CSM yellow warning.

6. What were the dose and regimen for the use of Primodos as a hormone pregnancy test and treatment for amenorrhea over the period it was available on the market in the UK?

Answer

We understand, based on historical literature, that when Primodos was first launched in the UK it was a presentation of 4 tablets each containing 10mg of norethisterone and 0.05mg of ethinyl oestradiol. Two tablets were to be taken on each of two consecutive days.

In 1960 it was re-formulated to become a presentation of 2 tablets each containing 5mg of norethisterone acetate and 0.01mg of ethinyl oestradiol. A tablet was to be taken on each of two consecutive days.

In 1963 it was re-formulated as a presentation of 2 tablets each containing 10mg of norethisterone acetate and 0.02mg of ethinyl oestradiol. A tablet was to be taken on each of two consecutive days.

By the time the product license of right provisions of the Medicines Act 1968 had come into force Primodos was not recommended for use as a pregnancy test and was recommended only for secondary amenorrhea not due to pregnancy. The recommended dose was 1 tablet on each of two consecutive days. The tablets still contained 10.0mg norethisterone acetate and 0.02mg ethinyl oestradiol.

7. We have heard that considerable numbers of free samples were given out up until 1970. Please can you provide any data you have on the distribution of free samples to healthcare practitioners, and the agreement with the CSD to cease the supply of free samples.

Answer

Bayer itself has no data on prescriptions of Primodos, but made available to the MHRA a copy of a report prepared in the early 1980s by Dr R.A. Wiseman of Schering Chemicals Ltd (see Answer to Question 5 above). It compared the historical trend in use of Primodos and Roussel's similar products in the UK (which together in most years accounted for 90% of total HPT sales) with the incidence of congenital malformations. This showed an absence of any correlations for malformations generally or specific types of malformation. Dr Wiseman's Report at Appendix 2 contains actual sales figure for both Schering's Primodos and Roussel's HPTs including samples distributed, but it does not provide any breakdown of these figures showing what samples were supplied by each company. In the disclosure made to the claimants in the litigation, it is apparent that in 1969 the CSD asked Schering Chemicals Ltd for information on samples of Primodos distributed and figures for January 1966 to June 1969 were provided by Schering as follows:

	1966	1967	1968	1969. Up to June
January	7,149 (incl last wk Dec. '65)	344	0	10
February	3,350	385	20	6
March	1,488	52	25	4
April	2,697	29	11	11
May	3,226	120	21	Nil
June	2,045	95	1	5
July	200	149	39	
August	955	66	7	
September	847	144	4	
October	630	156	16	
November	1,552	339	6	
December	1,400	500	0	
	25,539	2,379	150	36

We are aware that Schering took steps to reduce the supply of free samples of Primodos in the late 1960s but we are not aware of any discussion or agreement with the CSD that may have precipitated this step.

8. In the UK, was Primodos a prescription-only medication – for example, was it available from chemists as a test?

Answer

As far as Bayer is aware Primodos was at all times a prescription only product. The 1977 renewal of the product license of right recites that the product was also available as a P.O.M prior to 1964 when

the first non-statutory rules were being applied in advance of the 1968 Medicines Act. This will have precluded supply by a pharmacist other than pursuant to a doctor's prescription.

9. Were Schering aware of two studies carried out in 1960, one in Germany, one in Britain, which indicated that bleeding sometimes followed the administration of the test in women who were in fact pregnant? If so, what actions were taken in response to these studies?

Answer

We are not clear to which studies you are referring, nor do we know whether and when Schering became aware of particular studies. However, the claimants in the English litigation sought to strengthen their case on causation by suggesting that one plausible mechanism of action for the causation of malformations following administration of hormone pregnancy tests was the possibility that the product might induce occasional bleeding in pregnancy. Schering did not agree that this was plausible. The results of a study in Hungary to investigate this in women who had elected to terminate their pregnancy did not support the claimants' hypothesis and the investigators published the research (Pulkkinen 1984). The research is discussed at para 6.2.2 and 5.1.4.2 of the EWG Report.

Safety signals

10. The initial safety signal came in 1967 but no warning was issued in the UK until 1975. Please can you explain your response to the initial safety concerns, for example, clinical and epidemiological studies etc. With the benefit of hindsight, do you feel these studies were sufficient?

Answer

Bayer was not required to respond to any safety concerns relating to Primodos as it did not market this product. Nor is it able to speak in detail about the views held by Schering AG or Schering Chemicals about studies and events over 50 years ago that related to a company it acquired over 10 years ago. It can only refer you to the contemporaneous correspondence still in existence and now in the public domain and, in this respect, Bayer is in no better position than anyone else to interpret it. It is plain, however, from this correspondence that Schering spent considerable time with Dr Gal to assess the reliability of the data and it investigated the possibility of sponsoring its own large scale epidemiological study until it became apparent that others were already conducting substantial studies relevant to the same issue. Schering engaged with the regulatory authorities to explore what further work could usefully be done to follow-up the results of Dr Gal's research and it carried out further animal studies. As far as we are aware it was never suggested by the regulatory authorities in the UK or those anywhere else in Europe that these steps were insufficient.

11. In your last evidence you stated:

"at no time did Schering AG consider that the available pre-clinical, clinical and epidemiological evidence established a well-founded suspicion that use of Primodos in pregnancy increased the incidence of congenital malformation in the new-born. The conclusions of Schering and their scientists are entirely consistent."

a. Please can you provide any information detailing consideration of the risk/benefit profile once suspicions had been raised for both Schering, and Schering AG.

b. Given that there were non-invasive pregnancy tests available in the 1970s, was any suspicion of congenital malformation acceptable?

c. Would this be the same today?

Answer

Our statement about Schering AG's conclusions related to the issue of causation. In relation to the ongoing consideration by Schering AG and Schering Chemicals Ltd of risk-benefit issues, please see our answer to Q10 above. From the available correspondence, it is clear that there was a judgment to be made from time to time on risk-benefit issues and whether Primodos should continue to be recommended for use as a pregnancy test and/or for treatment of secondary amenorrhea not due to pregnancy. This also had regard to the advent and practical availability in the UK of urine immunological testing. By 1970, it is clear that Schering Chemicals had formed the view that there was a reasonable case that could be made for deletion in the UK of the pregnancy testing indication.

The McGregor Committee also held that view in 1970 and we provided the relevant correspondence to you in response to your previous questions. We note that the Committee did not refer to specific safety concerns or 'signals' and one must assume it was motivated solely by the principle that use of a drug in pregnancy could not be justified if alternative means of diagnosing pregnancy were now freely available. We have checked the British National Formulary of independent prescribing recommendations from that period and it first stated that combinations of oestrogens and progestogens such as Primodos should no longer be used in the early diagnosis of pregnancy in its 1971 edition. It related this advice to questions of reliability rather than safety and noted that such tests "have been superceded by urine tests". The same edition of the BNF made reference to the principles relating to the use of drugs in pregnancy and included a review of the drugs for which there was either evidence or suspicion that they could cause fetal damage. A number of products are mentioned, but there is no reference to exposure to sex hormones in pregnancy. Therefore, the available literature at that time was not interpreted by the relevant Committee responsible for the BNF entries as indicating the existence of a well-founded suspicion of risk associated with use of HPTs.

We are not able to speculate on how regulators would have approached this situation had it arose at different times in the decades that followed.

Indication change

12. Please can you explain why Primodos is absent from the February 1970 Edition (8) of the Proplist published by the McGregor Committee?

Answer

We do not know, but we note that the correspondence with the McGregor Committee previously provided to you shows that in February 1970 discussions with manufacturers of HPTs were still ongoing and it may well be that until the entry for Primodos was agreed (which appears to have been in March/April 1970) its inclusion in the Proplist of February 1970 was treated as premature.

13. When the McGregor Committee were deliberating removing the indication for pregnancy testing for all HPTs in 1970, did Schering engage in communications with other HPT manufacturers?

    Roussel removed their HPT from the market at this point, but Schering did not. Can you provide us with any information on the rationale for this?

Answer

We do not know what communications, if any, took place between Schering Chemicals Ltd and other manufacturers in the UK at this time. We are not aware of any correspondence at this time or reference to communications with competitors.

However, it is not correct that Roussel removed their similar product from the UK market in 1970. Roussel had a range of such products, including Amenorone, Amenorone Forte and Norone. Both Norone, and Amenorone Forte were expressly recommended for use as a pregnancy test and Amenorone only for amenorrhea. The product information for Amenorone Forte indicates that this product was promoted as stronger than Amenorone and designed for more rapid action. Norone was developed as a pregnancy test based on administration of two tablets taken as a single dose, while Amenorone Forte, involved administration of one tablet daily for 3 days. A historic document of Schering states that by 1967, Amenorone and Amenorone Forte had about 26% of the market in the UK. Amenorone Forte was seemingly Roussel's primary product for pregnancy testing and the competitor to Primodos. Norone was discontinued in January 1969 having been introduced only in 1966. In contrast, Amenorone Forte was not discontinued until 1977 (at the same time as Amenorone was discontinued). As with Primodos, Amenorone Forte was, following discussions with the McGregor Committee, only recommended for use for secondary amenorrhea.

14. We understand that during the 1960s the majority of Primodos use was as an HPT. Why did the sales figures keep going up once this indication had been removed? Were Schering aware of this, and if so, what action was taken regarding this off-label use?

Answer

As to the sales of Primodos for use as a pregnancy test, please see our answer at Q5. As one would expect where most use prior to 1970 seems to have been as a pregnancy test, sales of Primodos and Amenorone Forte progressively dropped after 1970. Dr Wiseman's Report referenced at Q 5 and 7 above notes that the rate of prescriptions based on MDI data rose from 1966 to 1970 and then fell progressively from 1970 to 1974 until discontinuation of these products in 1977/78. Actual sales (including samples distributed) for Schering and Roussel products fell from 581,000 packs in 1970 to 361,000 in 1974.

15. Contemporaneous documentation indicates there seems to be a difference in opinion over the continued marketing of Primodos between Schering UK and Schering in Germany. Please can you explain the reasons that the German view on the safety of Primodos prevailed.

Answer

Bayer can obviously give no first-hand evidence of the views on these issues held by personnel at Schering Chemicals Ltd or by personnel at Schering AG. It has no information other than that reflected by contemporary correspondence of the type appearing in the Berlin LandesArchiv. Schering AG specialised in the research and marketing of products based on sex hormones and their uses and had specialists in every relevant scientific discipline. Detailed reviews by regulatory bodies appear to have supported Schering AG's conclusion that there was not a well-founded suspicion that a causal connection existing between use of Primodos and an increased incidence of malformations in the newborn. Nevertheless, we note that Schering AG did not seemingly challenge its UK subsidiary's view in 1970 that the McGregor Committee's proposals should be accepted, and the pregnancy testing indication should be deleted, given the increased availability of urine testing in the UK.

Committee for the Safety of Drugs/Committee on the Safety of Medicines

16. There seems to have been a close relationship with the UK regulators, in particular Dr William Inman. Was this the case, and was this usual for the time?

Answer

Bayer has no first-hand knowledge of the relationship between Schering Chemicals Ltd or Schering AG and any regulatory bodies or personnel within those bodies. Bayer is aware of the correspondence between Dr Inman and Schering Chemicals Ltd which focused upon appropriate follow-up of the issues raised by Dr Gal. Dr Inman was a founder member of the Committee on Safety of Drugs (CSD) and was Principal Medical Officer at the Department of Health. He was from 1964 Medical Assessor of the Sub-Committee on Adverse Reactions of the CSD and from 1971 had the same position at the Committee on Safety of Medicines. He was responsible for the development of the pharmacovigilance "yellow card" system in the UK following the thalidomide tragedy. Dr Inman, therefore, had a particular responsibility for considering whether specific products were associated with side-effects/adverse events and the regulatory consequences if they were. It seems to us reasonable that Schering Chemicals would wish to liaise closely with him in relation to how they were responding to the issues raised by Dr Gal. In the past, pharmaceutical companies have sometimes been criticised for not sharing information with regulators and not engaging in a full and timely dialogue with regulators on safety questions. It seems that the relevant personnel at Schering Chemicals were assiduous on doing so and we do not view this as abnormal, particularly as the new regulatory framework prompted by the thalidomide tragedy was in its infancy and there was particular sensitivity about the use of drugs in pregnancy.

17. Dr Bill Inman of the Committee for the Safety of Medicines stated that it would have been irresponsible to recommend dramatic action over HPTs in 1972 as there were potential spin-offs for other treatment such as contraceptive pills. Was this a view shared by Schering at the time? What were the financial implications for potential changes to the contraceptive pill market?

Answer

Bayer does not know what views were held from time to time by Schering AG or Schering Chemicals Ltd in relation to the possible implications (including financial implications) of the debate about the safety of hormone pregnancy tests for other products based on sex hormones and, in particular, the oral contraceptive market.

18. Schering were notified of the study being carried out by the CSD/CSM which ran a pilot phase in 1969 and a full study from 1972-1973 (Greenberg et al, 1975 and 1977). Minutes from the meetings of the CSD/CSM indicate that they did not seem to be aware of the removal of the indication for pregnancy testing in February 1970. Did Schering take any actions to inform them of the indication change?

Answer

Bayer does not know what knowledge members of the CSD/CSM had about the change in the indications agreed by the McGregor Committee with manufacturers in 1970 or whether Schering Chemicals or other manufacturers had specifically drawn this change to the attention of CSD/CSM members. However, it seems unlikely that these bodies were unaware of the removal of the pregnancy test indication for these products as there were many of them and the revised indications were clear from MIMS and the ABPI Compendium of product information. Moreover when the product license of right from Primodos was first issued in 1971 pregnancy testing was not an approved indication.

19. In the UK, the first warning letters were sent out in 1975, five years after the removal of the indication for pregnancy testing. Who has responsibility for sending out a Dear Healthcare Professional letter regarding such off-label use?

Answer

In 1975, the European rules were focused upon the framework for approval of products. There was no provision describing the separate responsibilities of the holder of the marketing authorisation, save that if such holder himself decided to suspend marketing or withdraw a product from the market for reasons other than commercial reasons, he was required to notify the regulatory body forthwith.

The first European Directive specifically to address pharmacovigilance matters was not adopted until 1993 (Directive 93/39/EEC). It focused upon the responsibility of the company as the holder of the marketing authorisation to report to regulatory authorities for independent assessment adverse effects associated with its products that had been drawn to its attention by health professionals and related to the normal conditions of use i.e. use in accordance with the indications for which the product was recommended. The aim of reporting was so that regulators could adopt informed decisions on whether the authorisation should be varied, suspended or withdrawn and could seek to agree the steps to be taken with other Member State authorities. The UK had, in fact, already implemented similar provisions in the 1970s. However, it was only relatively recently that the holders of marketing authorisations have been required to monitor off-label use as part of their pharmacovigilance obligations.

In the 1970s, there was no EU or UK law defining who should send out a "Dear Doctor" letter regarding pharmacovigilance matters. National practice in relation to 'Dear Doctor' letters probably varied in the 1970s. In the UK holders of marketing authorisations and the relevant regulatory authorities would normally exchange information and collaborate in relation to the contents of any Dear Doctor letter that resulted from pharmacovigilance relating to a particular product. This is what appeared to have happened in 1975 in relation to the actions taken by the CSM in relation to use of Primodos and products like it for off-label use as a test for pregnancy.

Following a detailed review in 2012 of pharmacovigilance practices in the EU, Module X on safety communications which is part of the framework for good pharmacovigilance practices established

under EU legislation, has emphasised the need for a collaborative approach for "Dear HealthCare Professional Communications" (DHPCs) stating:

> *"The preparation of DHPCs involves cooperation between the marketing authorisation holder and the competent authority. Agreement between these two parties should be reached before a DHPC is issued by the marketing authorisation holder. The agreement will cover both the content of the DHPC (see XV.B.4.) and the communication plan (see GVP Annex II), including the intended recipients, the timetable and the channels for disseminating the DHPC."*

20. There were two uses indicated for Primodos in the UK, as well as anecdotal reports it was used in an attempt to elicit an abortion. Does Bayer have any data on the proportion of UK sales for the different uses?

Answer

Please see our answer to Q5 above.

21. In the letter Schering wrote to Dr Griffin at the CSM dated 25th October 1977, it was stated that 9.3% of the prescriptions for Primodos from July '76 to June '77 were for use as pregnancy tests. Please can you provide information on how this figure was obtained? [Please see Committee on Safety of Medicines file BN 116_24: https://mhra.filecamp.com/public/files/2qnc-h0brgtm2]

Answer

Bayer has no knowledge of how the figure you cite was arrived at for the percentage of the prescriptions written for Primodos in the year ended June 1977 that concerned its use as a pregnancy test. We assume it will have been based on statistics collated by market research bodies who were responsible for the widely used "Medical Data Index" figures that were based on monitoring of prescriptions written in the UK by a sample of GPs during a given week and reported quarterly. Dr Wiseman described the availability of such statistics in his report that is Annex 13 to the EWG Report.

Litigation

22. We have seen papers from the original litigation [*http://immdsreview.org.uk/downloads/Evidence/FOR%20PUBLICATION%20-%20Manufacturers%20of%20Hormone%20Pregnancy%20Tests.pdf*] which state that Schering had a wealth of experts, and we have heard that the plaintiffs struggled to recruit experts. It has been suggested that this disparity was due to the unequal spending ability of the two parties. Does Bayer have any information on what was paid to any of the experts involved in the litigation (including indirect payments such as research funding) during the 1970s and early 1980s.

Answer

Bayer has no first-hand knowledge of fees paid to expert advisors by either Schering or the Claimants. We understand from Mr Dodds-Smith whose then firm McKenna & Co was responsible for instructing experts for Schering that experts they instructed were paid consultation fees at the normal market rate. The claimants provided expert reports from a number of specialists, even though Schering addressed more discrete areas of science in their expert reports which were, therefore, more numerous. Therefore, any difficulty the claimants' lawyers had in recruiting experts is more likely related to the fact that fewer specialists in the scientific disciplines of relevance were comfortable supporting the claimants' case on causation having regard to their view of the science.

23. We note that Schering's solicitor, Ian Dodds-Smith, is listed as an author on a scientific paper related to the litigation. It strikes us as unusual, to have a lawyer as an author of a scientific paper. Do you have any comments on this?

Answer

This seems to be a misunderstanding. Ian Dodds-Smith did not act as a scientist. The paper in question related to an exercise of examination of base data underlying one of the main epidemiological studies relied upon by the claimants. It was undertaken in the course of preparation for the trial. This exercise was performed by Dr Richard Wiseman, Medical Director of Schering Chemicals Ltd and Mr Dodds-Smith. Mr Dodds-Smith's contribution was limited to the administrative task of checking the data, but in the interests of transparency both he and Dr Wiseman were named as co-authors.

24. Among the LandesArchiv material is pre-trial advice by Mr Clothier QC. He provides a pessimistic assessment of Schering's prospects of success and potential defences. Did Schering consider this a realistic appraisal of the situation? If not, please explain why not?

Answer

The advice in question of Mr Clothier QC is subject to legal privilege which has not been waived. It was given circa 1978 when the first claims were notified. After a series of pre-trial hearings the trial was subsequently scheduled to begin in 1982. Mr Clothier's advice was, therefore, not "pre-trial" advice in the normal sense of that expression, but rather was preliminary advice resulting from the first consultation that Schering had with an English Queens Counsel. At that time McKenna & Co., as instructing solicitors, had very little information about the history of the matter (the collection of all relevant documents for disclosure had not yet occurred) and the issues of causation had not been explored in any detail. Mr Clothier was provided with limited documentation that focused upon the correspondence between the Schering Chemicals Ltd and Schering AG following the publication of Dr Gal's study and he was asked to consider the reasonableness of Schering's conduct in the face of Dr Gal's study results.

Mr Clothier was not in a position to give a final view on this and his opinion notes that on several issues and for several periods that he had not yet been provided with relevant information. He noted that he had not seen any of the epidemiology on the subject and papers published up to mid-1970 would affect the potential exposure in negligence because they would be relevant to the continued evaluation of the benefit to risk ratio. He noted that primate studies had not yet been commissioned and he questioned why not. In fact, they were commissioned in several species and the results, showing no indication of teratogenicity, were ultimately published. Preliminary data mentioned by Mr Clothier on

secular trends comparing the sales trend for HPTs with the incidence of malformations proved later to be incomplete and misleading.

Moreover, Mr Clothier noted that he was not able to give an opinion on whether the possible exposure that he had identified from about mid 1970 concerning the labelling of Primodos would convert into liability because the claimants would have to prove causation. In respect of this he noted that he had seen none of the epidemiological studies or the broader scientific evidence. Mr Clothier was, therefore, not able to advise on either general causation or individual causation in cases yet to be chosen for trial by the claimants to illustrate their case.

Schering will no doubt have respected the advice given, even given its limitations, and shortly thereafter Mr Clothier ceased to practice at the bar. In the following years as Schering's legal team investigated the claims and the strength of its case on causation became apparent, it was clear that Mr Clothier's assessment had been unduly pessimistic. Schering ultimately instructed Mr Richard Rougier QC to prepare for the planned trial. By that time Schering had the benefit of the advice of some of the world's most experienced specialists in the scientific disciplines of relevance. They unequivocally supported Schering's case that there was no causal relationship between the use of sex hormones in pregnancy and the congenital abnormalities from which the claimants suffered. The transcript of the hearing to consider the claimants' application to discontinue the proceedings refers to the fact that Mr Rougier had indicated that in the light of all the investigations by Schering and preparations for trial that had occurred, were the case to go to trial Schering were confident that the claims would be defeated. That was also plainly the view of the claimants own counsel.

25. We note that the litigation was discontinued, not closed. Please explain the cost implications for both parties if the litigation were to restart.

Answer

The claims in the lead actions were discontinued in 1982. All other proceedings had been stayed pending the outcome of the lead actions. The claimants accepted that these other proceedings were dependant on the outcome of the lead actions and, therefore, discontinued these proceedings as well.

As noted in our answer to Q1, the permission of the Court would be required to recommence any of the claims in this old litigation which was essentially a group action with the illustrative claims chosen by the claimants.

The Court made it clear that it would only countenance recommencement if there had, in the meantime, been a material change in scientific knowledge and, therefore, a real prospect that the claims could succeed. There has been no such change in scientific knowledge and indeed today, unlike in 1982, the Court would have available to it the considered views of the UK regulatory authorities and the European Medicines Agency on the scientific issues and evidence.

In addition, the Court made it clear that it had decided to allow discontinuation rather than dismiss the claims because the claimants were children, and the claims were at that time within the statutory limitation period governing claims by children. That is not the case today some 37 years after the claims were discontinued. All such claims are now statute barred. Given the passage of time and the lack of availability of evidence from individuals with first hand knowledge of the research, development and marketing of Primodos in the 1950s to 1970s and the lack of availability of evidence from the regulatory bodies involved from time to time in relation to the history of Primodos and products like it, as well as the current view of the science expressed by regulators today, it seems highly unlikely that any new claims could be successfully pursued.

If for any reason the Court were to allow claims to proceed, the issue of the substantial costs incurred by Schering in relation to the original proceedings would arise for consideration against the above background. On discontinuation the Court ordered that the adult claimants should pay Schering's costs, but that the orders should not be enforced without the permission of the Court. Schering did not seek enforcement. Normally, in such circumstances, where the proceedings re-start, the defendants would expect to have their costs of the discontinued prior proceedings paid before the new proceedings commence. When the Court allowed discontinuation of the original proceedings in this case, the Judge decided not to impose any term as to the payment of Schering's costs before the proceedings could re-commence. However, he noted that any court asked to give permission for new proceedings, in its discretion, might well impose that term.

EMA reviews

26. In the last two years, there have been two separate Article 5(3) referrals to the EMA looking at the work of Professors Vargessen [sic] and Heneghan. We would appreciate your views on these papers, and the EMA reviews as well as on any potential implications this might have going forward.

Answer

The EMA's assessment of these two pieces of research is clear from the published opinions. In summary, the CHMP, which is the main expert scientific committee of the European Medicines Agency. was asked by the UK to give its opinion on the publication by Brown et al (2018) (in respect of which Professor Vargesson was a co-author) which concerned certain pre-clinical research in zebra fish involving exposure to the active substances of Primodos. It was asked to give an opinion on the zebrafish model for evaluating teratogenic effects in human pregnancy, the robustness of the study and on any clinical implications of the results in respect of the human foetus.

The CHMP was subsequently asked by the UK to give its opinion on a publication by Heneghan et al (2018) which concerned meta-analysis of old studies that had considered the use in pregnancy of oral hormone pregnancy tests containing norethisterone acetate and ethinyl oestradiol, and a potential association with an increased incidence of congenital malformations. The paper did not involve new data but rather a different method of analysis of existing data to that employed by the EWG. The CHMP's views were sought on the methodology employed in the paper and the clinical implications of the results, given that progestogens and oestrogens continue to be used in other medicines in the EU including oral contraceptives.

Brown et al (2018)

The CHMP Opinion was adopted on 18 October 2018. As we have noted in previous correspondence with you, the Safety Working Party of the CHMP determined that there are so many uncertainties and limitations concerning the zebrafish data that "the outcome of the study is not relevant for the human situation" and found that the "data available does not support a signal of teratogenicity of a combination of norethisterone and ethinyl oestradiol". The CHMP itself agreed and concluded that the zebrafish data did not give rise to any new clinical implications.

Heneghan et al (2018)

The CHMP Opinion was adopted on 26 April 2019. It was concluded that the results of the meta-analysis do not add new information to that contained in the detailed Expert Working Group Report

published by the UK's CHM and the EWG's conclusions remain valid. The CHMP added that as a result of the "multiple limitations of the meta-analysis study, the results described in this manuscript cannot be used to further expand clinical knowledge" and thus "have no clinical implications". The CHMP concludes:

> "*As a consequence, the conclusion that current clinical data available do not support a signal of teratogenicity of a combination of norethisterone/ethinylestradiol remain valid. The CHMP therefore did not recommend any further regulatory actions based on the above data*"."

Reviews by Bayer specialists agree with these criticisms and the conclusions that these two pieces of research have no clinical implications for existing products and do not undermine in any way the detailed review of the available scientific evidence conducted by the EWG on issues of causation or its reported conclusions.

ETHICON

PART OF THE Johnson & Johnson FAMILY OF COMPANIES

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

30th June 2019

Dear Dr. Valerie Brasse,

REF: IMMDS review – Written Questions to Ethicon – May 2019

Thank you for contacting Ethicon on 3. June 2019 to request our assistance in answering the Review's further questions.

We would like herewith to respond to your questions with the information below and attached.

We appreciate the opportunity to provide our response to the IMMDS review team.

Yours sincerely

Veronika Ruppik
Associate Director, Regulatory Affairs EU Strategy, Ethicon
[redacted]

Enc.

Product development

Question 1	The function of the TVT and TVT-O are similar. a. Why was the TVT-O developed? b. Was the risk/benefit profile the same? c. When you have two devices that have a similar function, but different risk profiles, will the device with higher adverse event levels remain on the market?

Response:

The CE Marking history of the TVT devices has been detailed in our original response to the Call for Evidence in October 2018, Attachment 1 (Section 2.4). TVT-O, Ethicon's second midurethral sling, was developed to provide pelvic surgeons with the option to use a transobturator midurethral sling to avoid the retropubic space and potentially reduce the risk of bladder, organ and vessel injury when treating patients for stress urinary incontinence. TVT-O built upon the framework laid down by a decade of work by Professor Ulf Ulmsten on the TVT combined with the investigation and ingenuity of Professor Jean de Leval, a well-known and respected Belgian surgeon. In 2002, Professor de Leval combined the TVT's proven Prolene polypropylene mesh and inside-first incision at the midurethra, with a surgical technique that instead followed a more lateral "Inside-Out" transobturator approach, which allowed for exact placement of the sling first at the midurethra and extending out through the transobturator space and exiting the inner thigh.

TVT and TVT-O have similar efficacy and safety profiles per the clinical data. The data continue to show that TVT-O is standard of care and a suitable midurethral sling option with efficacy similar to the gold standardTVT and has a low risk of complications. Surgeons will decide upon which midurethral sling to use based on their training and familiarity with the device but patient factors may influence their choice (such as midurethral closure pressure, hypermobility of the urethra, tissue quality, physical activity, previous surgeries, etc.). Many surgeons continue to utilize the retropubic TVT device and prefer it to be a part of their armamentarium. There are various reasons including that it is the gold standard and most-studied stress urinary incontinence surgical option with the longest follow up out to 17 years as discussed in our original response at Attachment 1.[1] Other reasons include their comfort with the device, their long history of use of the TVT and seeing it help so many women with burdensome SUI; their use of the device in certain patient populations such as patients with ISD or LUPP, obesity, those patients with recurrent SUI, etc. What is clear is that the TVT is safe, effective, durable, well-studied, and needed to ensure that surgeons have options to choose from to meet each patient's clinical needs. In summary, TVT and TVT-O have similar efficacy and safety profiles. However, based on factors such as surgeon training and experience, midurethral closure pressure, hypermobility of the urethra, tissue quality, physical activity, previous surgeries, etc. surgeons may prefer to use one over the other when they individualize treatment of the patients.

As we have explained above, although similar, these two products provide different benefits and some surgeons favour one over the other. The mere fact that one or more products within a particular family of products may have a different risk profile(s) to another does not of itself mean that one or more of them should be discontinued or withdrawn from the market. As here, each

[1] Bakas P, et al. Assessment of the long-term outcome of TVT procedure for stress urinary incontinence in a female population: results at 17 years' follow-up. Int Urogynecol J. 2019 Feb;30(2):265-269; Braga A, et al. Tension-free vaginal tape for treatment of pure urodynamic stress urinary incontinence: efficacy and adverse effects at 17-year follow-up. BJU Int. 2018 Jul;122(1):113-117; Nilsson CG, et al. Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. Int Urogynecol J. 2013 Aug;24(8):1265-9.

Question 1	The function of the TVT and TVT-O are similar. a. Why was the TVT-O developed? b. Was the risk/benefit profile the same? c. When you have two devices that have a similar function, but different risk profiles, will the device with higher adverse event levels remain on the market?

may have benefits specific to it/them, or may be the preferred product by one section of the healthcare provider profession, as we have outlined in more detail above. Providing a range of treatment options for surgeons and patients is important. Surgeons must consider the specific benefits and risks of each product based on the patient's medical condition and the surgeon's medical experience and discuss the options with the patient prior to surgery.

Question 2	We understand from documents in the Batiste case that Professor Ulf Ulmsten had filed a US patent application for the TVT in February 1997 and that J&J had agreed to pay circa $1 million for the rights, providing that the second trial of the TVT which Prof. Ulmsten conducted, validated the initial study findings. Is this correct? This has been raised by patient groups, and others, as a conflict of interest. Is it standard practice to fund trials where the chief investigator has an interest?

Response:

Thank you for the opportunity to correct this understanding. With respect to Prof. Ulmsten, a leading researcher in Sweden, he studied what would become the TVT over many years. He conducted a study on TVT on his own group of 75 patients and published the two-year data in 1996. As part of Ethicon's due diligence in licensing the TVT product in 1997, Ethicon was interested in evaluating evidence that the TVT device would be safe and effective and that Prof. Ulmsten's results could be replicated in the hands of other surgeons in other institutions. To this end, there was a milestone payment of $400,000 included in the TVT License and Supply Agreement which was payable if other surgeons had similar results to that published by Prof. Ulmsten. This type of milestone payment is common where the intellectual property at issue (here the TVT) shows an increased value and utility. While it was impressive that TVT was revolutionary and worked in Prof. Ulmsten's hands, Ethicon wanted to see if the device would be helpful to other surgeons and their patients. Otherwise Ethicon would not want to overpay for intellectual property that had limited use. As a result, several surgeons from six different medical institutions participated in the Scandinavian multi-center trial that was the subject of the 1998 study.[2] Prof. Ulmsten's center was just one of the study centers. None of the trial centers received any financial support from Ethicon for conducting this study. The results of the work of those surgeons were consistent with Prof. Ulmsten's initial findings and demonstrated that the TVT device and the procedure to implant it held immense value to the broader medical community separate and apart from the surgical skills of its inventor. Both studies were published in the International Urogynecology Journal, which is a peer reviewed journal that is one of the preeminent journals in this field. In the twenty years that have passed since the study was published in 1998, hundreds of clinical studies, systematic reviews and metaanalyses with no connection to Prof. Ulmsten or Ethicon have evaluated the clinical performance of TVT, further validating its safety, effectiveness, broad utility, and value.

[2] Ulmsten U, Falconer C, Johnson P, Jomaa M, Lannér L, Nilsson CG, Olsson I. A multicenter study of tension-free vaginal tape (TVT) for surgical treatment of stress urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 1998;9(4):210-3.

Question 3	The minutes from the SERNIP meeting of 12 January 2000 state that Ethicon had challenged SERNIP over the classification of the TVT. The TVT went from class C to class A. Please can you provide details of this challenge and the evidence supplied to SERNIP. We have been told that no peer reviewed research papers were presented, just conference abstracts, please can you confirm if our information is accurate.

Response:
Given the amount of time that has passed, our investigations to date have not enabled us to identify the contemporaneous documentation presented to SERNIP. However, we can confirm that there were peer reviewed papers on TVT in the public domain at the time including the Ulmsten and Petros papers concerning the design and development of TVT, Professor Ulmsten's 1996 single center study and the TVT 1998 multicenter study[3], as well as:

1. Nilsson CG. The tension free vaginal tape procedure (TVT) for treatment of female urinary incontinence. A minimal invasive surgical procedure. Acta Obstet Gynecol Scand Suppl 1998;168:34-7
2. Wang AC, Lo TS. Tension-Free Vaginal Tape: A Minimally Invasive Solution to Stress Urinary Incontinence in Women. J Reprod Med 1998;43:429-434
3. Paparella P, De Santis L. A study of tension-free vaginal tape (TVT) in association with Lahodny's urethrocystopexy for the surgical treatment of stress urinary incontinence in patients with severe urethrocystocele. Urogynaecologia Int J 1999;13(2):65-70
4. Olsson I, Kroon U. A Three-Year Postoperative Evaluation of Tension-Free Vaginal Tape. Gynecol Obstet Invest 1999;48(4):267-9
5. Ulmsten U, Johnson P, Rezapour M. A three-year follow up of tension free vaginal tape for surgical treatment of female stress urinary incontinence. Br J Obstet Gynaecol 1999 Apr;106(4):345-50
6. Maltau JM, Verelst M, Holtedahl KA, Due J. A new minimally invasive surgical method for stress incontinence in women. Tidsskr Nor Laegeforen 1999 Jun 20;119(16):2342-5
7. Primicerio M, De Matteis G, Montanino Oliva M, Marceca M, Alessandrini A, Caviezel P, Tocci A. Use of the TVT (Tension-free Vaginal Tape) in the treatment of female urinary stress incontinence. Preliminary results. Minerva Ginecol. 1999 Sep;51(9):355-8

[3] Ulmsten U, Ekman G, Giertz G, Malmström A. Different biochemical composition of connective tissue in continent and stress incontinent women. Acta Obstet Gynecol Scand. 1987;66(5):455-7; Petros PE, Ulmsten UI. An integral theory of female urinary incontinence. Experimental and clinical considerations. Acta Obstet Gynecol Scand Suppl. 1990;153:7-31; Petros PE, Ulmsten UI. An integral theory and its method for the diagnosis and management of female urinary incontinence. Scand J Urol Nephrol Suppl. 1993;153:1-93; Ulmsten U, Petros P. Intravaginal slingplasty (IVS): an ambulatory surgical procedure for treatment of female urinary incontinence. Scand J Urol Nephrol. 1995 Mar;29(1):75-82; Falconer C, Ekman-Ordeberg G, Malmström A, Ulmsten U. Clinical outcome and changes in connective tissue metabolism after intravaginal slingplasty in stress incontinent women. Int Urogynecol J Pelvic Floor Dysfunct. 1996;7(3):133-7; Ulmsten U, Henriksson L, Johnson P, Varhos G. An ambulatory surgical procedure under local anesthesia for treatment of female urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 1996;7(2):81-5; discussion 85-6; Ulmsten U, Falconer C, Johnson P, Jomaa M, Lannér L, Nilsson CG, Olsson I. A multicenter study of tension-free vaginal tape (TVT) for surgical treatment of stress urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 1998;9(4):210-3

Question 4	It has been suggested that the follow up periods for medical devices are too short. a. What long term follow up has Ethicon conducted on your pelvic mesh products? b. Is this still ongoing for products that are no longer marketed?

Response:
Ethicon has conducted long term follow up and review of its products since their inception. This began with studies analysing Prolene polypropylene, the unique biomaterial used in these devices, in the 1960s. With regard to the TVT and POP mesh products, Ethicon performs systematic review of the medical literature and conduct post-market surveillance to assess performance, safety and efficacy of these mesh products indefinitely, following their launch. As discussed above and in the original responses there are a plethora of data on the devices, which includes long term follow up studies. Ethicon has also funded or provided support for studies with longer follow up of devices such as the TVT Ward Hilton study[4], the TVM studies that assessed Gynemesh PS and the prototype of the Prolift device[5], investigator-initiated studies on Prolift[6], and the company sponsored Prosima study.[7]

Question 5	Is Ethicon involved (either directly or indirectly) in databases or registries designed to actively monitor patients' post-implantation of a mesh device? If not would this be of interest to you?

Response:
Ethicon has a team dedicated to evidence generation and has always supported and monitored independent and company sponsored research on its products. Ethicon believes that there is value to data generation concerning its devices and has been involved in registries pertaining to some of its pelvic mesh devices. For example, Ethicon provided support for a French prospective database registry concerning the TVT-O device in 2005, the year after its introduction in France, which included safety data from 86 centers on consecutive patients.[8] Ethicon also conducted a multicentre company-sponsored registry that collected data on the TVT, TVT-O and TVT Secur

[4] Ward K, et al. Prospective Multicentre Randomised Trial of Tension-Free Vaginal Tape and Colposuspension as Primary Treatment for Stress Incontinence. BMJ, 2002. 325:67; Ward KL, Hilton P; UK and Ireland TVT Trial Group. A prospective multicenter randomized trial of tension-free vaginal tape and colposuspension for primary urodynamic stress incontinence: two-year follow-up. Am J Obstet Gynecol. 2004 Feb;190(2):324-31; Ward KL, Hilton P; UK and Ireland TVT Trial Group. Tension-free vaginal tape versus colposuspension for primary urodynamic stress incontinence: 5-year follow up. BJOG. 2008 Jan;115(2):226-33.
[5] Miller D, Lucente V, Babin E, Beach P, Jones P, Robinson D. Prospective clinical assessment of the transvaginal mesh technique for treatment of pelvic organ prolapse-5-year results. Female Pelvic Med Reconstr Surg. 2011 May;17(3):139-43; Jacquetin B, Hinoul P, Gauld J, Fatton B, Rosenthal C, Clavé H, Garbin O, Berrocal J, Villet R, Salet-Lizée D, Debodinance P, Cosson M. Total transvaginal mesh (TVM) technique for treatment of pelvic organ prolapse: a 5-year prospective follow-up study. Int Urogynecol J. 2013 Oct;24(10):1679-86.
[6] Gutman RE, Nosti PA, Sokol AI, Sokol ER, Peterson JL, Wang H, Iglesia CB. Three-year outcomes of vaginal mesh for prolapse: a randomized controlled trial. Obstet Gynecol. 2013 Oct;122(4):770-7; Milani AL, Damoiseaux A, IntHout J, Kluivers KB, Withagen MIJ. Long-term outcome of vaginal mesh or native tissue in recurrent prolapse: a randomized controlled trial. Int Urogynecol J. 2018 Jun;29(6):847-858.
[7] Sayer T, Lim J, Gauld JM, Hinoul P, Jones P, Franco N, Van Drie D, Slack M; Prosima Study Investigators. Medium-term clinical outcomes following surgical repair for vaginal prolapse with tension-free mesh and vaginal support device. Int Urogynecol J. 2012 Apr;23(4):487-93.
[8] Collinet P, Ciofu C, Costa P, Cosson M, Deval B, Grise P, Jacquetin B, Haab F. The safety of the inside-out transobturator approach for transvaginal tape (TVT-O) treatment in stress urinary incontinence: French registry data on 984 women. Int Urogynecol J Pelvic Floor Dysfunct. 2008 May;19(5):711-5.

Question 5	Is Ethicon involved (either directly or indirectly) in databases or registries designed to actively monitor patients' post-implantation of a mesh device? If not would this be of interest to you?

devices.[9] Smaller prospective, observational, multi-centre registries were sponsored by Ethicon on the Prosima and Prolift +M devices.[10]

Recently, the American Urogynecologic Society (AUGS) initiated a new SUI registry concerning midurethral slings, which was submitted to Ethicon's Investigator Initiated Study Committee. Ethicon decided to partially sponsor this trial (IIS # ETH-16-208) at the specific request of AUGS leadership, [redacted]

The largest registries come from countries whose health system is set up in such a way as to allow for the monitoring of each patient. Several studies using these registries have been published over various points in time, including very early in the life of the TVT device such that data in thousands of patients was captured and reported.[11] Furthermore there have been numerous other database studies which include hundreds of thousands of patients which report on midurethral slings including studies with longer term follow up.[12]

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[9] Tincello DG, Botha T, Grier D, Jones P, Subramanian D, Urquhart C, Kirkemo A, Khandwala S. The TVT Worldwide Observational Registry for Long-Term Data: safety and efficacy of suburethral sling insertion approaches for stress urinary incontinence in women. J Urol. 2011 Dec;186(6):2310-5.

[10] Khandwala S, Slack M, Hinoul P, Urquhart C, Al-Salihi S. A trocar-free procedure for vaginal prolapse repair using mesh and a vaginal support device - an observational registry (Prosima). Female Pelvic Med Reconstr Surg. 2011 Sept/Oct;17(5) Supp. 2: S164; Khandwala S, Lucente V, Van Drie D, Gauld J, Hinoul P. Clinical outcomes of an observational registry utilizing a trocar-guided mesh repair of vaginal prolapse using partially absorbable mesh (Prolift+M) Female Pelvic Med Reconstr Surg. 2011 Sept/Oct;17(5) Supp. 2: S163-164.

[11] Tamussino KF, et al. (Austrian registry) Tension-free vaginal tape operation. Results of the Austrian registry. Obstet Gynecol 2001;98:732-736; Kuuva N, et al. (Finland registry) A nationwide analysis of complications associated with the tension-free vaginal tape (TVT) procedure. Acta Obstet Gynecol Scand 2002;81:72-77; Kolle D, et al. (Austrian registry) Bleeding complications with the tension-free vaginal tape operation. Am J Obstet Gynecol 2005;193:2045-2049; Ammendrup A, et al. (Danish registry) Urinary Incontinence Surgery in Denmark from 2001-2003. Int Urogyn J 2006;17(Suppl 2):S110; Tamussino K, et al. (Austrian Registry) Transobturator tapes for stress urinary incontinence: Results of the Austrian registry. Am J Obstet Gynecol 2007:197:634.e1-634.e5; Dyrkorn OA, et al. TVT compared with TVT-O and TOT: results from the Norwegian National Incontinence Registry. Int Urogyn J 2010:21:1321-1326; Nilsson M, et al. (Swedish Registry) Female urinary incontinence: patient-reported outcomes 1 year after midurethral sling operations. Int Urogyn J 2012;23:1353-1359; Sottner O, et al. (Czech registry) Surgical treatment of female stress urinary incontinence through years 2007-2011. Report of National Registry. Int Urogyn J 2013;24(Suppl 1):S55-S56; Svenningsen R, et al. (Norwegian registry) Long-term follow-up of the retropubic tension-free vaginal tape procedure. Int Urogyn J 2013 Aug;24(8):1271-8; Hansen MF, et al. (Danish Registry) Repeat surgery after failed midurethral slings: a nationwide cohort study, 1998-2007. Int Urogyn J 2016 Jul;27(7):1013-9; Kurkijarvi K, et al. Surgery for stress urinary incontinence in Finland 1987–2009. Int Urogyn J 2016;27:1021-7; Morling JR, et al. Adverse events after first, single, mesh and non-mesh surgical procedures for stress urinary incontinence and pelvic organ prolapse in Scotland, 1997-2016: a population-based cohort study. Lancet. 2017 Feb 11;389(10069):629-640; Engen M, et al. (Norwegian registry) Mid-urethral slings in young, middle-aged, and older women. Neurourol Urodyn 2018;37:2578–2585; Hansen MF, et al. A Danish national population-based cohort study of synthetic midurethral slings, 2007–2011. Int Urogyn J 2018 Aug 2. doi: 10.1007/s00192-018-3719-y; Kurkijärvi K, et al. Reoperations for Female Stress Urinary Incontinence: A Finnish National Register Study. Eur Urol Focus. 2018 Sep;4(5):754-759.

[12] Jonsson Funk M, et al. Sling revision/removal for mesh erosion and urinary retention: long-term risk and predictors (188,454 women in US Thomson Reuters MarketScan Commercial Claims and Encounters and Medicare Supplemental Coordination of Benefits database). Am J Obstet Gynecol. 2013 Jan;208(1):73.e1-7; Welk B, et al. Removal or Revision of Vaginal Mesh Used for the Treatment of Stress Urinary Incontinence (59,887 women from Ontario, Canada). JAMA Surg. 2015 Dec;150(12):1167-75; Keltie K, et al. Complications following vaginal mesh procedures for stress urinary incontinence: an 8 year study of 92,246 women (Hospital

Question 5	Is Ethicon involved (either directly or indirectly) in databases or registries designed to actively monitor patients' post-implantation of a mesh device? If not would this be of interest to you?

Continuously monitoring and collecting data is a regulatory obligation that Ethicon takes very seriously. Ethicon anticipates that the extensive amount of data already available, including long term data from different countries and databases in hundreds of thousands of patients, and the understanding that various professional societies are collecting data which will likely be published, may simply refine and confirm already-existing insights regarding long-term safety and efficacy. In addition, the company remains open to further discussions with regards to any new registry design and content based on the scientific merit.

Question 6	Questions have been raised over the appropriateness of the information supplied to doctors. It has been reported[13] that there was an email in 2009 from the associate medical director at Ethicon, which suggested that the wording be changed for three Ethicon Gynecare TVT mesh implants, explaining: "From what I see each day, these patient experiences are not 'transitory' at all." We understand the IFUs were updated to reflect this in 2015, why was there a delay?

Response:
This inquiry concerns a specific litigation matter which has been taken out of context and for which we do not intend to comment on other than to say that our IFUs have been reviewed by pelvic surgeons and determined to be adequate to the intended reader, the pelvic surgeon, given their education, training and experience as outlined in our original response at Attachment 6.

Question 7	The latest NICE guidance[14] recommends the use of brightly coloured mesh. In your previous evidence you stated that "*Initially the TVT mesh was made using clear Prolene Mesh. In 2001, Ethicon created TVT Blue Prolene mesh, which is identical in construction to the clear Prolene mesh with the exception of the change in pigmentation with the addition of blue striping. This change enhanced the intraoperative visibility of the mesh*." Were all of your pelvic mesh products blue from 2001 onwards?

Response:
Blue mesh was added to the Ethicon POP and TVT products beginning in 2002.

Episode Statistics database). Sci Rep. 2017 Sep 20;7(1):12015; Gurol-Urganci I, et al. Long-term Rate of Mesh Sling Removal Following Midurethral Mesh Sling Insertion Among Women With Stress Urinary Incontinence (95,057 women from NHS hospitals in England). JAMA. 2018 Oct 23;320(16):1659-1669; Cashman S, et al; BAUS Section of Female Neurological and Urodynamic Urology. Results of the British Association of Urological Surgeons female stress urinary incontinence procedures outcomes audit 2014-2017. BJU Int. 2019 Jan;123(1):149-159.

[13] https://www.independent.co.uk/news/uk/home-news/vaginal-mesh-scandal-tvt-transvaginal-sling-implant-risks-thalidomide-device-bbc-panorama-a8102726.html

[14] https://www.nice.org.uk/guidance/ng123

Question 8	It appears from emails sent by [redacted] at Gynecare that visibility of mesh and mesh fragments was an issue. Did the change in colour lead to a higher level of reporting of adverse incidents? If so, what action did you take in response?

Response:
The intention behind incorporating a pigmented blue fiber into the knitted mesh was to provide increased visibility in the surgical field. We have not identified any escalations or field actions that determined that a change in color was the reason behind any higher level of reporting of adverse events.

Question 9	Please explain how you respond to concerns from clinicians. For example, it has been widely reported that some UK based clinicians raised concerns about the lack of evidence around the efficacy and safety profile of Prolift[15].

Response:
Ethicon properly evaluated and studied its POP and TVT products before they were placed on the market. These devices are among the most studied products of their type in the world. Ethicon applies the extensive research it collects among products with the same types of materials and/or surgical techniques. With regards to Prolift, as discussed in the original response at Attachment 2, over 700 patients had been studied with Gynemesh PS or Transvaginal prolapse mesh (TVM), which are comprised of the same mesh material as Prolift, before the launch of Prolift and additional company sponsored studies were also underway. Since then numerous clinical studies, including randomized controlled trials, have been conducted as discussed in our original response. The most recent Cochrane review did not find a statistically significant increased risk of dyspareunia or adverse change in sexual function as assessed by questionnaire scores with POP mesh compared to non-mesh POP repair.[16] Similar results were seen in the Society of Gynecologic Surgeons systematic review.[17] More recently, and since our original response, a comprehensive meta-analysis of 17 RCTs including 2,976 patients (1,488 patients with transvaginal mesh POP repair and 1,488 patients with native tissue POP repair) showed that sexual function and de novo and postoperative dyspareunia were similar between the patients who underwent TVM repair and those who underwent native tissue repair.[18] As we earlier pointed out, dyspareunia and pain are risks of all POP surgeries that pelvic surgeons are familiar with, and the highest-level data do not show an increased risk with Prolift and TVM.

[15] https://www.theguardian.com/society/2018/nov/27/vaginal-mesh-implant-sold-despite-warnings-could-cause-pain-johnson-johnson

[16] Maher C, Feiner B, Baessler K, Christmann-Schmid C, Haya N, Marjoribanks J. Transvaginal mesh or grafts compared with native tissue repair for vaginal prolapse. Cochrane Database Syst Rev. 2016 Feb 9;2:CD012079. doi: 10.1002/14651858.CD012079; Maher C, Feiner B, Baessler K, Christmann-Schmid C, Haya N, Brown J. Surgery for women with anterior compartment prolapse. Cochrane Database Syst Rev. 2016 Nov 30;11:CD004014. doi: 10.1002/14651858.CD004014.pub6.

[17] Schimpf MO, et al. Graft and Mesh Use in Transvaginal Prolapse Repair: A Systematic Review. Obstet Gynecol. 2016 Jul;128(1):81-91.

[18] Liao SC, et al. Changes in Female Sexual Function After Vaginal Mesh Repair Versus Native Tissue Repair for Pelvic Organ Prolapse: A Meta-Analysis of Randomized Controlled Trials. J Sex Med. 2019 May;16(5):633-639.

Question 10	We understand that your reps provide training for surgeons in how to correctly utilise products, including during surgery. What actions do you as a company take to ensure that the patients are fully aware and consent?

Response:
Your understanding is incorrect. Ethicon sales representatives do not provide surgeon training. They provide information from Ethicon on the safe and effective use of our products. Ethicon also provides educational materials including surgeon monographs and technique guides, anatomic models and surgical videos. Surgeon training on the use of Ethicon's pelvic mesh devices is provided by Ethicon through contracts with skilled surgeons. All discussions regarding treatment options and patient consent are between the practicing pelvic surgeon and his or her patient.

Question 11	Once a device has been removed from the market what obligations are there for you as the producer to continue to carry out post-marketing surveillance? What reassurance can you offer women already implanted with a device that is no longer marketed that any longer-term consequences will be monitored?

Response:
Post-market surveillance (PMS) continues indefinitely for long term implants. PMS reports continue to be generated and monthly monitoring of complaints continues.

Question 12	Do you undertake explant studies? If so please detail what you examine and any common findings on the following a. Histology b. Inflammatory responses c. Changes in structure of the mesh

Response:
Ethicon does explant mesh in its preclinical studies in various animal models which it uses in its assessment of a product's biocompatibility and mechanical properties. Ethicon has conducted hundreds of preclinical explant studies in various animal models which show Prolene-based meshes elicit a tissue response consistent with a biocompatible mesh. This response is described as an initial acute inflammatory response that is followed by chronic inflammation/foreign body response that resolves to a minimal to mild response, along with minimal to mild fibrosis surrounding the mesh fibers.

Ethicon has also provided funding in the form of an Investigator Initiated Study grant for a prospective study to evaluate the histological inflammatory response to a macroporous polypropylene transvaginal mesh used for pelvic organ prolapse surgery (Gynemesh PS / Prolift).[19] The combined results of the clinical and histological inflammatory evaluation suggested that biocompatibility was satisfactory.

There is no significant unintended change in the structure of the mesh assessed in the preclinical studies. Because of the macroporous structure of the mesh, tissue grows into the mesh. The structure does change by design in mesh with a partially absorbable component such as Monocryl

[19] Elmer C, Blomgren B, Falconer C, Zhang A, Altman D. Histological inflammatory response to transvaginal polypropylene mesh for pelvic reconstructive surgery. J Urol. 2009 Mar;181(3):1189-95

Question 12	Do you undertake explant studies? If so please detail what you examine and any common findings on the following a. Histology b. Inflammatory responses c. Changes in structure of the mesh
in Ultrapro mesh, as the Monocryl dissolves over time leaving the macroporous Prolene polypropylene as the permanent material implanted.	

Question 13	Please can you detail for the record your position on any potential link between polypropylene pelvic mesh and a. autoimmune conditions b. cancers
Response: There is no reliable link between Ethicon's polypropylene pelvic mesh and cancer or autoimmune conditions. Several epidemiologic studies have been conducted which demonstrate that there is a naturally occurring incidence of cancer and autoimmune conditions in patients and Ethicon's polypropylene pelvic mesh devices do not cause or significantly increase the risk of cancer or autoimmune conditions.[20] A large cohort study on cancer that included almost 21,000 women with a midurethral sling who were compared to a large cohort showed no significant association between women with a midurethral sling and primary cancer in any organ system when compared with women without midurethral sling.[21]	

US

Question 14	In the US, TVT was approved 28th January 1998 on the basis of substantial equivalence to the Boston Scientific ProteGen Sling. The ProteGen sling was recalled for safety reasons on 22nd January 1999. In their enforcement report, the FDA said there was a higher than expected rate of vaginal erosion and dehiscence, and that the device 'does not appear to function as intended'. Were you aware of this recall, and what actions were taken in response to it?
Response: Yes, Ethicon is aware of the recall of the ProteGen sling. The clinical efficacy and safety of Ethicon's TVT device was based on its own evaluation over a period of many years as described in the original response at Attachment 1. Although the ProteGen sling was listed as a predicate device for TVT, the clinical efficacy and safety of Ethicon's TVT device was based on its own evaluation. The conditions that ultimately led to ProteGen's recall stemmed from the device's differences from TVT, not its similarities. These conditions specifically included the material from	

[20] Altman D, et al. Cancer Risk After Midurethral Sling Surgery Using Polypropylene Mesh. Obstet Gynecol. 2018 Mar;131(3):469-474; Chughtai B, et al. Challenging the Myth: Transvaginal Mesh is Not Associated with Carcinogenesis. J Urol. 2017 Oct;198(4):884-889; Chughtai B, Sedrakyan A, Mao J, Eilber KS, Anger JT, Clemens JQ. Is vaginal mesh a stimulus of autoimmune disease? Am J Obstet Gynecol. 2017 May;216(5):495.e1-495.e7; Linder BJ, et al. Evaluation of the local carcinogenic potential of mesh used in the treatment of female stress urinary incontinence. Int Urogynecol J. 2016 Sep;27(9):1333-6; King AB, et al. Is there an association between polypropylene midurethral slings and malignancy? Urology. 2014 Oct;84(4):789-92.

[21] Altman D, et al. Cancer Risk After Midurethral Sling Surgery Using Polypropylene Mesh. Obstet Gynecol. 2018 Mar;131(3):469-474

Question 14	In the US, TVT was approved 28th January 1998 on the basis of substantial equivalence to the Boston Scientific ProteGen Sling. The ProteGen sling was recalled for safety reasons on 22nd January 1999. In their enforcement report, the FDA said there was a higher than expected rate of vaginal erosion and dehiscence, and that the device 'does not appear to function as intended'. Were you aware of this recall, and what actions were taken in response to it?

which ProteGen was made (including bovine collagen) and the manner in which it was used (anchored to the pelvis with bone screws).

Ethicon continues to monitor, collect and evaluate the clinical evidence on the performance and safety of the TVT from a range of sources. The TVT which uses a macroporous Prolene polypropylene mesh that is placed without tension (no bone or suture anchors) via a small midurethral incision has been shown to be the most biocompatible material for SUI surgery, and the data on TVT do not show a high rate of vaginal erosion and dehiscence. To the contrary, as discussed more at length in the original response at Attachment 1, these data which include long term studies have consistently found a 1-3% mesh exposure rate.[22] For example, the Cochrane Review by Ogah et al. found that monofilament tapes like the TVT family of products had higher objective cure rates compared to multifilament tapes, and the monofilament tapes also had fewer tape erosions (TVT 1.3% versus 6% for multifilament tapes). A systematic review of medium and long term studies of midurethral slings was published in 2015 which included 49 studies and all but one study included an Ethicon TVT family product, documenting that they are by far the most studied and longest studied devices.[23] For the retropubic slings, there were numerous long term studies (See Tables 1-2) and the TVT represented the vast bulk of the data (Table 3: 3,801 TVT patients out of the total 3,974 total retropubic midurethral sling group). The rate of mesh exposure for TVT (the retropubic group) was 2.1% which included over 25 studies that assessed TVT between 5 and 17 years of follow up. These data are consistent with the 2.1% rate reported in the more recent Cochrane Review by Ford et al. and additional 17 year TVT studies as referenced in the original response. The data and evidence from hundreds of studies show the utility, durability, safety and efficacy of the TVT device and that the concerns seen with ProteGen are not present with the TVT.

[22] Ogah J, Cody JD, Rogerson L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD006375; Novara G, Artibani W, Barber MD, Chapple CR, Costantini E, Ficarra V, Hilton P, Nilsson CG, Waltregny D. Updated systematic review and meta-analysis of the comparative data on colposuspensions, pubovaginal slings, and midurethral tapes in the surgical treatment of female stress urinary incontinence. Eur Urol. 2010 Aug;58(2):218-38; Schimpf MO, Rahn DD, Wheeler TL, Patel M, White AB, Orejuela FJ, El-Nashar SA, Margulies RU, Gleason JL, Aschkenazi SO, Mamik MM, Ward RM, Balk EM, Sung VW; Society of Gynecologic Surgeons Systematic Review Group.. Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. Am J Obstet Gynecol. 2014 Jul;211(1):71.e1-71.e27; Tommaselli GA, Di Carlo C, Formisano C, Fabozzi A, Nappi C. Medium-term and long-term outcomes following placement of midurethral slings for stress urinary incontinence: a systematic review and metaanalysis. Int Urogynecol J. 2015 Sep;26(9):1253-68; Ford AA, Rogerson L, Cody JD, Ogah J. Mid-urethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2015 Jul 1;(7):CD006375. Update in: Cochrane Database Syst Rev. 2017 Jul 31;7:CD006375; Fusco F, Abdel-Fattah M, Chapple CR, Creta M, La Falce S, Waltregny D, Novara G. Updated Systematic Review and Meta-analysis of the Comparative Data on Colposuspensions, Pubovaginal Slings, and Midurethral Tapes in the Surgical Treatment of Female Stress Urinary Incontinence. Eur Urol. 2017 Oct;72(4):567-591

[23] Tommaselli GA, Di Carlo C, Formisano C, Fabozzi A, Nappi C. Medium-term and long-term outcomes following placement of midurethral slings for stress urinary incontinence: a systematic review and metaanalysis. Int Urogynecol J. 2015 Sep;26(9):1253-68.

Question 15	The recent decision by the FDA (16 April 2019) to remove mesh for the transvaginal repair of anterior compartment prolapse due to a lack of sufficient evidence of safety. This has heightened concerns among patient groups that other products which had previously had market approval may also be found to have insufficient evidence of safety. What reassurance can you offer them?

Response:
The FDA has determined that the manufacturers who were seeking pre-market approval had not demonstrated reasonable assurance of safety and effectiveness for these transvaginal prolapse devices, which is the premarket standard that now applies to them since the agency reclassified them into class III (high risk) in 2016. While Ethicon has not marketed transvaginal prolapse mesh devices since its voluntary discontinuation of the devices in 2012, Ethicon met all regulatory requirements during the time these products were available. Patients can be confident in the products due to the extensive scientific data on the Ethicon transvaginal prolapse mesh devices and Ethicon's continuing postmarket surveillance of these devices. See also response to Question 16 below.

Question 16	On 3 January 2012 the FDA ordered all manufacturers of mesh products for transvaginal POP to undertake 522k studies, including PS120043, PS120044, PS120045, PS120046 and PS120095. We note that your last reply did not contain details of any completed 522k studies. Please can you explain why these studies do not appear to have been completed.

Response:
Ethicon had already invested in evidence generation on the safety and efficacy of its products. A business decision led to the global discontinuation of the transvaginal POP devices. With the discontinuation of these devices the FDA agreed that Ethicon did not need to complete the 522 studies. As discussed at length in our original response and above, there is extensive data including long term data on our devices. For example, another recent long term Prolift study was published since our original response, which showed that at 8.5 years follow up the mesh-related complication rate (including mesh exposures, infections, and retractions requiring surgery) was 4.3%, the urinary incontinence rate was 5.7%, the prolapse recurrence rate was 7.2% and for total Prolift, the reoperation rate for prolapse recurrence was only 4%.[24] Physicians can rely on the vast body of evidence on the Ethicon POP and TVT products.

Question 17	We have heard from patient groups that they would welcome a US style 'Sunshine Payment Act' over here in the UK. Please can you describe your experiences of 'Sunshine Payment Act' and whether you would support the introduction of a similar system here.

Response:
As you may know, the Physician Payments Sunshine Act of 2009 provides for transparency in the relationship between physicians and applicable manufacturers with respect to payments and other

[24] Pécheux O, Giraudet G, Drumez E, Di Serio M, Estelle JD, De Landsheere L, Cosson M. Long-term (8.5 years) analysis of the type and rate of reoperation after transvaginal mesh repair (Prolift®) in 349 patients. Eur J Obstet Gynecol Reprod Biol. 2019 Jan;232:33-39.

Question 17	We have heard from patient groups that they would welcome a US style 'Sunshine Payment Act' over here in the UK. Please can you describe your experiences of 'Sunshine Payment Act' and whether you would support the introduction of a similar system here.

transfers of value and physician ownership or investment interests in manufacturers. No such similar legislation exists in the UK.

However, Ethicon, through its parent company, is a member of the MedTech Europe, which is the European trade association for the medical technology industry including diagnostics, medical devices and digital health.
The devices industry discloses financial relationships (Fee for service arrangements, invitations to company organised events that include travel and lodging) with HCPs to the employer or relevant competent authority, prior to the engagement. *Transparent MedTech* is the MedTech Europe centralised transparency platform where the industry discloses all financial contributions provided to independent medical education.
The platform publishes the following types of contributions to medical education:

- educational grants to support Third Party Organised Educational Events (including attendance of HCPs, support of faculty (e.g. speakers) as well as support to the general running of the event);
- scholarships and fellowships;
- and grants for public awareness campaigns.

MedTech Europe members are responsible for the information they publish in this platform. Currently, the system covers countries that are members of the European Union (including the United Kingdom). See https://www.ethicalmedtech.eu/transparent-medtech/ for further details.

In the United Kingdom, Ethicon is member via its affiliated company Johnson & Johnson Medical Device of the ABHI, Association of British HealthTech Industries Ltd.
ABHI promotes ethical compliance across all their members through their ABHI Code of Ethical Business Practice so that healthcare professionals and the public can have confidence in the integrity of the industry. All members of ABHI are obliged to sign up to the code.
The Code is self-regulatory and is designed to increase transparency of payments made to healthcare professions by medical manufacturers based in Europe. The most recent Code of Practice is released in July 2018 and a link is provided here.
https://www.ethicalmedtech.eu/wp-content/uploads/2017/06/ABHI-Code-of-Business-Practice-final-July-2018.pdf

Litigation

Question 18	There have been many pelvic mesh MDLs in the USA. J&J appeared more reluctant to settle than other manufacturers. Was this the case? And if so, why?

Response:
For this response J&J refers to its 01 May 2019 10-Q Quarterly report filing with the United States Securities and Exchange Commission, which states, in part, as follows:
"Claims for personal injury have been made against Ethicon, Inc. (Ethicon) and Johnson & Johnson arising out of Ethicon's pelvic mesh devices used to treat stress urinary incontinence and

Question 18	There have been many pelvic mesh MDLs in the USA. J&J appeared more reluctant to settle than other manufacturers. Was this the case? And if so, why?

pelvic organ prolapse. The Company continues to receive information with respect to potential costs and additional cases. Cases filed in federal courts in the United States have been organized as a multi-district litigation in the United States District Court for the Southern District of West Virginia. The Company has settled or otherwise resolved a majority of the United States cases and the costs associated with these settlements are reflected in the Company's accruals. … The Company has established accruals with respect to product liability litigation associated with Ethicon's pelvic mesh products."

Question 19	Have Ethicon used alternative summary reporting repository for any of their pelvic mesh devices? If so, please may we have details? Do similar unpublished reporting provisions running in parallel to publicly accessible databases apply in other jurisdictions?

Response:
While adverse events are typically reported individually into the FDA's MAUDE database, the FDA allowed manufacturers to submit summary reports for well-established issues for which independent reports would not provide additional information to help FDA understand the nature of the risk, and summary reporting would allow FDA to track the frequency of occurrence. FDA also permitted summary reporting to report large numbers of injury claims received in litigation, where we may not have enough information to complete individual reports. Alternative summary reports were used in the mesh litigation for this reason. It's important to understand that the purpose of summary reporting was to allow FDA to review reports of well-established risks more efficiently. Summary reporting was not allowed for patient deaths and unusual, unique or uncommon adverse events, which have always been submitted to FDA individually and are publicly visible on the FDA web site. Adverse events and malfunctions reported to the FDA, regardless of the reporting mechanism, have always been used by Ethicon and the FDA to assess the safety of our products as part of a comprehensive post-market surveillance program.
The US FDA sunset its alternative summary reporting program for all manufacturers and all devices in May 2019. As a result, Ethicon has started to report all complaints on a rolling basis, as it has done for those complaints not covered under the previous exemption.

Ethicon has no summary reporting in place according to MEDDEV 2.12-1 (Rev. 2001, Section 5.5.7) in the EU.

Regarding the second part of this question, Ethicon reports all applicable adverse event complaints according to the national or regional regulatory requirements. Ethicon's previous exemption for alternative summary reporting in the US did not affect its obligation to report the same complaints according to other jurisdictions' regulations, if required.

Future

Question 20	Do you feel that the new EU medical device regulations are satisfactory? If not what would you like to see changed?

Response:
Ethicon has always followed the highest standard of regulatory review. We welcome the new Medical Device Regulation (MDR).

Question 21	The new EU MDRs impose a higher level of post-market surveillance on manufacturers. What tools and methodologies will be used to fulfil these requirements and how will this differ what is currently applied?

Response:
Johnson & Johnson Medical Devices Companies has established an EU Medical Devices Regulations (MDR) Program tasked with achieving EU MDR compliance.

Our internal tools and methodologies are proprietary and confidential and as a result we will not disclose them here.

Question 22	There have been several schemes which have been set up to provide redress (not compensation) to patients with implantable medical devices, such as the ASR hip scheme. Please can you explain the circumstance which you would consider might merit the application of such a redress scheme.

Response:
In our response (dated 24 October 2018) to question 18 of the original set of questions posed by the Review Committee, we commented briefly on certain schemes run in some Nordic countries and elsewhere. Your question here is narrower and addresses non-compensatory schemes, citing the ASR Reimbursement Programme.

This ASR Reimbursement Programme was introduced following a voluntary world-wide recall of a particular design of hip replacement medical device, known as the ASR™ Hip System.

The circumstances surrounding our pelvic mesh products are fundamentally different from the voluntary ASR recall. Ethicon continues to offer pelvic mesh devices for the treatment of stress urinary incontinence, which is a procedure endorsed by urogynecological associations around the world, including the British Society of Urogynaecologists. As is explained in more detail elsewhere in these and our earlier responses, these devices are backed by years of clinical research, have undergone rigorous regulatory reviews and have been chosen by millions of women seeking relief from often debilitating pelvic conditions.

Question 23	We have heard from patient groups who have lost trust in all organisations involved in implanting medical devices, including manufacturers. What do you think can be done to resolve this? What actions are you currently taking to do so?

Response:
Ethicon is part of the Johnson & Johnson family of companies. At the heart of Johnson & Johnson's business decisions lies its Credo, (https://www.inj.com/credo/), which has guided Johnson & Johnson for 75 years and guides all decision making and policies (https://www.ini.com/about-ini/policies-and-statements). The company, through its workforce of over 130,000 employees, strives to improve the health of humanity. We hold ourselves to the Credo and our company policies, standards, guidelines, procedures and code of conduct. We operate with the highest standards regarding our employees, the environment, the patients and consumers we serve, and all other stakeholders. Our Ethical Code for the Conduct of Research and Development is intended to complement our Credo by providing more specific standards of conduct and behavior for physicians, clinical research scientists and others who are responsible for medical aspects of research and development.

Teams comprised of employees with expertise in science, product development, surgery and other disciplines evaluate the devices both before and after they are marketed. The monitoring, device assessment and risk-benefit analysis processes are maintained in accordance with current regulatory and industry standards. The processes assess the utility, functionality and safety of the device, with different vehicles including conducting safety assessments that assess potential failure modes and causes, reviewing legacy, preclinical and/or clinical data, and carefully assessing the benefits and risks before launching a product.

We have in place the J&J Office of the Chief Medical Officer, a global group of medical and scientific professionals focused on advancing evidence- and science-based decision-making that is driven by bioethical principles and values. We also have formal processes involving committees of experts who perform governance reviews and provide input on how R&D teams should evaluate and enhance the safety profile at the product development stage. Day-to-day safety reviews and decisions related to product safety are made by multidisciplinary safety management teams.

Our sector Medical Safety Councils, which are chaired by the sector Chief Medical Officers, manage more complex safety assessments and decisions. The Johnson & Johnson Medical Safety Council, chaired by the Johnson & Johnson Chief Medical Officer, advises as needed and sets standards and policies related to medical safety. Our R&D groups submit all required information to regulatory health authorities across the globe for products that require regulatory review, including results of clinical trials and other documentation describing the safety and efficacy profile of our products. Regulatory authorities examine these data to establish whether the benefits of a product outweigh potential risks and decide whether to approve the product for marketing.

After commercialization, we continue active surveillance to monitor for potential safety issues by conducting post-marketing studies using real-world data (RWD), continuously reviewing potential adverse event (safety) information and using advanced technologies to help respond rapidly and appropriately, in close partnership with regulatory authorities and other stakeholders, to issues that may arise. We also develop risk management plans that are regularly reviewed and updated when additional safety information becomes available as more people use our products over a

Question 23	We have heard from patient groups who have lost trust in all organisations involved in implanting medical devices, including manufacturers. What do you think can be done to resolve this? What actions are you currently taking to do so?
longer period of time. Where appropriate, we work with regulatory authorities to update product labels.	

ETHICON
PART OF THE Johnson&Johnson FAMILY OF COMPANIES

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

16th July 2019

Dear Dr. Valerie Brasse

REF: IMMDS review – Questions to Ethicon 8 July 2019

Thank you for contacting Ethicon on 8. July 2019 to request our assistance in answering the Review's further questions.

We would like herewith to respond to your questions with the information attached below.

We appreciate the opportunity to provide our response to the IMMDS review team.

Yours sincerely

Veronika Ruppik
Associate Director, Regulatory Affairs EU Strategy, Ethicon
[redacted]

Enc.

ETHICON
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Question	Response
Can I just confirm that Ethicon are content for us to publish this further evidence on our website (Once it has been through our own legal checks) as we have done with the earlier evidence supplied by the company.	Yes, we confirm.
On a separate issue, we have heard from a number of clinicians that the rapid take up of mesh in the early years as the 'gold standard' for the treatment of SUI and pelvic organ prolapse was in part a direct result of the aggressive marketing of these products by the manufacturers. How does Ethicon respond to this? Are you able to describe Ethicon's marketing strategy for Gynaecare and other Ethicon mesh products?	We cannot comment on the practices of other manufacturers. Ethicon disagrees strenuously with any insinuation that it aggressively marketed these devices. Ethicon's support for the introduction of pelvic mesh devices was responsible and appropriate for new devices that surgeons did not have previous experience implanting. Professional education courses were taught by qualified surgeon faculty and were important in ensuring the safe and effective use of products, as well as knowledge of the recommended surgical techniques. Professional education courses were provided to accommodate the high volume of surgeons who requested training because they saw the value of the procedure for their patients. The reference to TVT and midurethral slings as well as sacrocolpopexy mesh in the medical community as the "gold standard" occurred over time as extensive clinical data, including level 1 studies, were published supporting the efficacy of the devices combined with widespread surgeon preference for implanting mesh, which resulted in pelvic mesh becoming standard of care. Please refer to our original response to the Call for Evidence, question 3, provided in October 2018.
Was it, for example, standard practice to offer financial or other non pecuniary benefits to clinicians to attend training events? If so, how has this changed over the last decade?	No, there was no offer for financial or other non pecuniary benefits to clinicians to attend training events. The travel costs and incidentals such as meal costs spent in connection with attending a training event could be covered by the company and/or reimbursed, consistent with standard industry and business practice. Please also refer to our responses from 30 June 2019 to Question 17.

British Paediatric Neurology Association and the Royal College of Paediatrics and Child Health

- Published guidance on ‘Prescribing valproate to female patients under 18 years of age’ https://www.rcpch.ac.uk/sites/default/files/2019-04/bpna_rcpch_valproate_guidance_130419_0.pdf

Care Quality Commission

Received by email:

We committed to following up on a request made by Sir Chantler during our evidence session.

Dear Sir Cyril,

Thank you very much indeed for asking me to describe the links between the Care Quality Commission (CQC) and NHS England/Improvement in terms of our future work together to improve patient safety following the evidence session I attended with my colleague, Dr Nigel Sparrow, at the Independent Medicines and Medical Devices Safety Review.

The CQC directly monitors and inspects the quality of care provided by organisations, taking enforcement action where necessary. Safety is one of our five key priority areas and we also respond directly to risks highlighted by staff, patients and their families.

I apologise for the delay in replying to you but wanted to await publication of “The NHS Patient Safety Strategy: Safer culture, safer systems, safer patients” as it references many of the areas that CQC has been focussing on over recent years and will continue to support alongside NHS England/Improvement to improve safety.

Our 2018 publication on never events, “Opening the door to change: NHS safety culture and the need for transformation”, set out 5 recommendations:

1. NHS Improvement and Health Education England should work together to develop a common curriculum and basis for patient safety education, training and ongoing development.

2. That the development of the national patient safety strategy should ensure that the NHS has safety as its top priority.

3. There should be leaders in patient safety in NHS Trusts

4. There should be standardisation of clinical processes, equipment and governance where these could benefit from standardisation.

5. The national patient safety alert committee (NaPSAC) should oversee a new patient safety alerts system that aligns the processes and outputs of all bodies and teams that issue alerts.

The new NHS patient safety strategy addresses almost all of these areas and describes the regulatory role of the CQC in supporting the strategy areas such as NaPSAC reporting and in the wider monitoring and inspection of the safety in organisations registered with the CQC.

As a specific example of collaborative working, the CQC publication “The state of care in mental health services 2014-2017” identified safety as the biggest concern for mental health services. The NHS Improvement Mental Health Safety Improvement Programme (MHSIP) aims to provide both bespoke support to mental health trusts on their individual safety priorities as well as support around challenges that are common across many or all local systems. The MHSIP works with the 54 NHS trusts providing mental health services in England, and closely with CQC centrally and with CQC and NHS Improvement teams regionally. This programme includes a trust engagement programme through which the MHSIP team meet every trust executive team to discuss the CQC report following inspection of the trust.

Before this meeting the MHSIP team meet the regional CQC and NHS teams to develop a shared understanding of each organisation’s safety concerns. The MHSIP team then work with the trust to determine priority areas and to devise an improvement plan.

We also continue to work closely on improvements to safety in the independent health sector including our publication this year of “Driving improvement: Case studies from eight independent hospitals”. Professor Ted Baker, CQC Chief Inspector of Hospitals, presented the findings from this publication at the recent Independent Health Providers Network (IHPN)/CQC joint conference in June. The conference included the IHPN’s update on the Medical Practitioner Assurance Framework (formerly known as the Consultant Oversight Framework). The work of the IHPN and CQC continues and the following evaluation comment demonstrates how this approach is being valued by the sector:

“I am pleased to see the collaboration between CQC and IHPN as this is vital in today’s healthcare community.”

I hope that this summary shows the collaborative work that is both in place and in development between the CQC and NHS England/Improvement as well as an update on the progress of the work that the CQC is doing with the IHPN.

With best wishes,

Nigel,

Nigel Acheson MD PGCert (Patient safety and clinical risk management) FRCOG SFFMLM

Deputy chief inspector of hospitals, Care Quality Commission

MHRA

The MHRA answered further follow-up questions posed by the Review:

1. *Email from the Review to the MHRA reads: As you are probably aware NICE are about to amend their guidelines on the management of urinary incontinence and pelvic organ prolapse to make the overlap with IPG 599 clearer – and in particular to remove the continuing confusion about the continuation of the ' research only context' restriction in the use of trans vaginal mesh for the treatment of prolapse. It will also recognise the change in the market availability of the relevant CE marked products.*

   In my exchange with NICE about this they pointed out that IPG 599 is not affected by the change in product availability as non CE certified products can be used in in procedures restricted to research only, provided those products have been authorised by the MHRA.

   Can you tell more about this [Specific questions below]

1.1 What processes does the MHRA use to approve these devices and how do these processes relate to the EU wide notified body CE certification?

Our written evidence to IMMDSR question 20 covers this process but we have added the relevant text below for convenience.

A manufacturer must meet many requirements prior to obtaining a CE mark. They must also hold clinical data to support claims made for all types of medical devices. This clinical data is set out in a clinical evaluation, which is an assessment and analysis of clinical data to verify the clinical safety and performance of the device. Typically, a clinical evaluation will include a clinical investigation specific to the device where a medical device has new design features or uses new materials. Under UK law the manufacturer must inform MHRA if a clinical investigation in the UK is planned, and they must provide all relevant documents for a robust assessment by MHRA of the safety and performance of the device. The assessment will determine if MHRA has an objection or no objection and whether the proposed clinical investigation can be carried out in patients in the UK. We have issued guidance on this process: notify MHRA about a clinical investigation for a medical device, clinical investigations of medical devices – guidance for investigators and clinical investigations of medical devices – guidance for manufacturers.

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

The notified body role is in the assessment and verification of the above clinical evaluation reports and supporting documentation provided by the manufacturer to support demonstration of conformity of a device with the Essential Requirements of the relevant Directive for the purpose of CE marking.

1.2 *How many such devices have been authorised by the MHRA for this 'research only' purpose – and of those how many, if any, are mesh devices for use in pelvic surgery?*

In 2018, we received 81 clinical investigations applications and following the process above, we approved 62 so they could start in the UK. No applications have been received for mesh for pelvic surgery (to treat stress urinary incontinence or pelvic organ prolapse).

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

1.3 *Are these approvals time limited and does the MHRA impose post use monitoring requirements out with the research studies themselves?*

Yes. The manufacturer must make an application to MHRA at least 60 days before the investigation is due to begin, and such a clinical investigation may only proceed provided no grounds for objection are raised by the MHRA within the 60-day time limit.

Also, there are time limits in the trial design/protocol for how long the trial will take and must be justified by them and accepted by us.

Regarding post use monitoring, the trial researchers or sponsors shall send us serious adverse events that occur during the clinical investigation for review. These events undergo a clinical and technical review on a weekly basis for all clinical investigations conducted in the UK. If concerns are raised, we will contact the researchers and take action where required. For example, we can pause or a suspend a clinical investigation.

Also, the trial protocol should include proposed follow-up period with justification and where applicable, details of any proposed post-market clinical follow-up plan and provision of long-term safety and performance data of the device under investigation.

1.4 *In the absence of tailored CE marked products for transvaginal repair of prolapse, how far could another CE approved mesh product be adapted for use in these procedures without requiring further regulatory approval?*

Broadly speaking, where the intended purpose of use and/or design of a CE marked device has changed to include transvaginal repair of prolapse, it would require the device to meet the requirements of the Directive and undergo an appropriate conformity assessment by a notified body to obtain a CE mark for this new intended use.

Any modification to a CE-marked device or using it in any other way not described in the manufacturer's label and instructions for use, would be considered 'off-label'. We have issued 'Off-label use of a medical device' guidance which says users should follow the manufacturer's instructions for use. It also gives information when there is no option but to use a device off-label and what steps to take, including getting approval from MHRA for exceptional use of non-CE marked devices (see below).

1.5 *Is there an equivalent 'off label' categorisation for devices?*

The term usually relates to CE-marked devices. However, the researchers should use the device as intended and in accordance with the requirements in the trial protocol. The

protocol must also include suitable methods to make sure the protocol is being followed. We must be notified of all study deviations and any proposed corrective actions should also be provided.

1.6 Would the MHRA know the extent of it?

Off-label use is not generally reportable by the manufacturer under the vigilance system unless death or a serious injury occurred.

Whether intentional or not, off-label use does occur with a wide range of CE-marked devices.

Off-label use should be considered by the manufacturer as part of the pre and post market phase to reduce this risk as far as possible, and for example could lead to improvements in the instructions for use or change in design.

Exceptional use
To note, there is another situation where a non-CE marked device or use of an existing CE-marked device for a different purpose can be used on humanitarian grounds. This is called 'exceptional use'.

A manufacturer (with agreement from the patient's clinician) can apply to supply a medical device that does not comply with the law (does not have a CE mark) for the treatment of a single named patient if there is no legitimate alternative available. This is called an exceptional use of a non-CE marked medical device. Our guidance shows how a manufacturer can apply for approval to supply a non-compliant medical device.

Exceptional use' applications are normally for a single patient. There is also the 'derogation' that could also be used for multiple patients.

As outlined in our email dated 22 May 2019 whilst there is no direct supply/distribution in the UK of surgical mesh for the treatment of prolapse, healthcare providers can import CE-marked devices intended for this use from outside of the UK. If there is a CE-marked device available, we may not grant approval for exceptional use.

2.1 There can be no clinical investigations in the UK – for which read the use of a non CE marked device as part of a device clinical trial ie research only -without the UK's competent authority ie the MHRA determining that it has no objection to the trial taking place on patients in the UK. I assume that covers both NHS and private patients.

Correct – all UK clinical investigations must have approval (no objection) from MHRA before they start and covers all UK patients.

However, if a hospital wants to do an 'in-house' study where they have manufactured a medical device in-house for their own patients with no intention get a CE mark - they don't need to notify MHRA.

If they then want to provide a medical device to another organisation or see the potential to get a CE mark themselves (that up until now has been manufactured in-house for their own patients) for data to support safety and performance of a commercial product, they will have to notify MHRA to seek approval to conduct a clinical investigation.

2.2 The MHRA therefore has a full database of these non-CE device applications and their outcomes? Is this database openly accessible?

For UK clinical investigations we have an internal database with UK applications and associated documents including our decision to reject or accept an application.

It is not publicly accessible.

2.3 How is knowledge of these clinical investigation applications and outcomes shared between EU countries?

For clinical investigations across Europe including the UK, EUDAMED (European Databank on Medical Devices) the competent authority adds details of these and records their decisions to reject or accept an application.

This databank serves as a central repository for information exchanged between national competent authorities and the European Commission. It is not publicly accessible.

2.4 How many successful mesh clinical investigation applications have there been, if not in the UK, in other EU countries?

As mentioned above, the databank is not publicly accessible, so we are unable to give this information.

Furthermore, clinical investigation information is exempt from disclosure under section 44 of the Freedom of Information Act (FOIA) as detailed below.

2.5 If a clinician routinely uses a CE marked device for its intended purpose but not in accordance with the manufacturer's instructions is that considered 'off-label' whether or not the device has been modified in any way?

It is off-label use.

Our guidance says 'you should use medical devices as described by the manufacturer in the instructions. If you use the device in any other way, it's considered 'off-label' use'.

2.6 How many manufacturers/ other reports of death or serious injury have there been following 'off-label' use of pelvic mesh products in the UK?

Since 2015, there have been no reports of death in which off-label use was reported.

Since 2015, there have been three reports of serious injury from members of public of off-label use and one report from a healthcare professional. No conclusions have been drawn to confirm if off-label use caused the injury.

FOI Act Section 44 – Prohibitions on disclosure: the release of information is exempt as its disclosure is prohibited by other legislation. In this case, section 237 of the Enterprise Act 2002 prohibits a public authority from releasing information which came to it in connection with the exercise of its functions, and which relates to the affairs of an individual or business.

The MHRA is satisfied that the information you have requested:

- constitutes information which came to us in connection with the exercise of the Agency's functions. MHRA has a duty of consumer protection under the Consumer Protection Act 1987 which is listed as a specified function under Schedule 14 of the Enterprise Act 2002 and receives information while exercising consumer protection functions in its role as the regulator of medicines and healthcare products.
- relates to the affairs of businesses which continue to exist.

On this basis, we are satisfied Section 44 of the FOI Act applies and the information is exempt from release.

Section 44 of the FOIA is an absolute exemption and is not subject to the public interest test. If you disagree with how we have interpreted the Freedom of Information Act 2000 with regards to your request, you can ask for the decision to be reviewed. The review will be carried out by a senior member of the Agency who was not involved with the original decision.

2.7 Regarding the off-label usage of pelvic mesh devices and reports of deaths/serious injuries, do you have the comparable data for pre 2015?

Between 2010 and 2014 inclusive the following shows the number of reports relating to surgical mesh to treat stress incontinence or pelvic organ prolapse:

- No reports of death in which off-label use was reported.
- Reports of serious injury in which off-label use was reported:

Report source	Number	Conclusions
Member of public	0	n/a
Healthcare professional	2	- *Foreseeable side effect (see below)* - *Use error (unintentional foreign body retention)*
Manufacturer	1	Not confirmed.

Broadly speaking, the data since 2010 does not show systematic off-label use reported to MHRA, or the cause of adverse events associated with the use of surgical mesh for the treatment of SUI or POP.

2.8 Also are you able to explain why no conclusions [in previous response] were drawn as to whether the serious injuries were caused by the off-label usage of the devices in question?

All the reports were sent to the manufacturer. The three reports since 2015 which indicated off-label use occurred showed no conclusions could be drawn because:

- Two of the reports were reviewed by the manufacturer. They found inadvertent organ perforation had occurred, but there was no evidence to confirm off-label use was a contributory factor.
- The third event was a non-reportable event as described below. No further information was obtained.

To note, reports that are considered to be expected foreseeable side effects listed in the manufacturer's instructions for use are not usually reportable under the post market surveillance vigilance system as described in our written evidence. We would not routinely expect a final report from the manufacturer. Nonetheless, a manufacturer is required by the legislation to systematically monitor and analyse all adverse events (reportable or not to MHRA) to assess the post-market experience with their devices and take action as necessary.

2.9 How are these investigated?

See our written response to IMMDSR Q2 for detailed information on how we collect, process and investigate device related adverse events (page 23).

It should be noted, an 'investigation' can take many forms to establish why something happened and/or to take further action to reduce the risk of it occurring again. Such as:

- examining the device by the manufacturer
- reviewing batch release information to ensure the device met design and manufacturing specifications
- gaining more information on an individual event
- analysing similar events to look for patterns/trends

As stated in our written evidence we do not routinely investigate individual incidents in which we obtain a final report from the manufacturer, and definitive conclusions drawn to explain why something went wrong. A similar approach taken by NHS Improvement.

However, we use a range of data and place a robust level of scrutiny on monitoring the safety and performance of medical devices so that appropriate action can be taken quickly. The information we gather from all reports (with and without conclusions found), along with other data sources such as scientific papers, correspondence from the public, and hospital episodes statistics for admitted patient care, outpatient and A&E data, build up a better picture of what is happening. This helps us spot issues/trends as they emerge so we can act upon them quickly and reduce the risk of harm to others, a process which is called 'signal detection'[1].

[1] A signal is an indication from any source which suggests a concern regarding one or multiple medical devices and justifies subsequent action. One report may trigger a signal and, on some occasions,, it requires several incidents to identify a signal.

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

Potential action may result in:

- a MHRA medical device alert giving safety advice to the healthcare service
- generic guidance like the off-label publication
- the use of social media to notify the public about a safety issue
- sharing information with other organisations in the healthcare system for action and learning (including the Medical Device Safety Officer Network as described in our evidence – see page 23)
- the manufacturer makes appropriate design changes, improves instructions for use or issues a recall notice (called a field safety notice) to remove the devices or batch of devices from use.

These types of actions help to reduce the risk of similar reports occurring again to protect patient and public health.

3. *Following MHRA providing an update on the FDA order regarding surgical mesh for transvaginal repair of anterior compartment prolapse, the Review asked the MHRA for UK-specific information.*

3.1 *Does the MHRA know how many other suppliers, other than Boston Scientific and Coloplast, provide mesh for use in the UK for the repair of anterior transvaginal prolapse?*

Further to your email, MHRA has been contacting a number of manufacturers of surgical mesh to establish the UK status in supply. As there is no central mechanism for collecting what the UK is/was using (including within the private sector) we cannot be sure if we have contacted all manufacturers. Nonetheless, to the best of our knowledge, there is no supply of surgical mesh for transvaginal repair of POP (anterior and posterior) to the UK by any manufacturer/supplier/distributor.

Coloplast will continue to supply the EU to the end of September 2019, but the UK has not purchased any of these devices since 2016.

Of the manufacturers contacted, they confirm this status will not change if the pause is lifted. Of course, new products or new distributors to the UK may change this overall status, and if the device is CE marked then surgeons could purchase these devices from outside of the UK.

For a sub-group of women with recurrent prolapse and/or previous failed surgery the alternative surgical option is native tissue repair or off-label use (use of another mesh not intended for this indication – which has liability issues associated with it).

There is availability in supply of other POP devices (abdominal/laparoscopic) and SUI devices to the UK.

We have kept DHSC informed.

With regards to our previous reference to NICE guidance, it is our understanding from discussions with NICE, that the 'research only' recommendation within NICE IPG599 is current, so you may wish to confirm with NICE.

4. *Notifications of refusal by a notified body for a CE marking when the refusal was based on safety issues.*

4.1 *How many such notifications has the MHRA received over the last 10 years and how many of those relate to surgical mesh products for the treatment of SUI and POP?*

We do not analyse the data to provide the number of refusals we receive from notified bodies in the UK or refusals uploaded onto EUDAMED. It is not possible to collect this data, particularly where information was received outside of EUDAMED.

4.2 *Under the current Regulations the MHRA would not know if there had been a previous refusal by an EU notified body for the same mesh products on the sale in the UK. Is that correct?*

That is correct. As mentioned in our earlier response, regrettably there is currently no harmonised approach across Europe for refusal of CE applications by an EU notified body. We receive such information from some competent authorities but not all.

To address these points, we welcome the new Regulations to strengthen the requirements for uploading information onto EUDAMED and into the notified body module.

5. *Updates on the Heneghan et al meta-analysis*

The EMA published its review of the Heneghan et al meta-analysis, available here.

MHRA has published the CHM expert group report and minutes of the 18 March meeting, available here.

6. *Updates on the Pregnancy Prevention Programme*

A revised Annual Risk Acknowledgment Form was published in April this year and the information is in the public domain. The amendments were made as a result of feedback from patient and healthcare professional stakeholders and the main change was to include a section of the form to be completed if the PPP is not applicable (ie if the woman if not of childbearing potential). I attach a link to the current form:

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/794114/Valp-ARAF-March-2019.pdf.

7. *Between 2010 and 2018 there were 6 reports to the MHRA of serious injury arising from off label use of pelvic mesh for treatment of SUI and/or prolapse.*

7.1 *Since off-label usage covers both the use of pelvic mesh for purposes other than was intended and the use of pelvic mesh other than in strict compliance with the manufacturers' instructions is this likely to be an underestimate?*

As mentioned in our written response to Q4, academic research into patient safety incidents reported to official reporting systems compared to those identified by various other means is reported to range from 1% and 50% depending on definition and method. We have not done any further studies in the medical device area, so it is important we supplement this with other data sources such as electronic health records, registries, Health Episode Statistics.

7.2 *Are you satisfied that healthcare professionals fully understand the definition of off label usage?*

We have guidance available to help healthcare professionals understand what is meant by off label use. Similar guidance was previously given via a Medical Device Alert and was disseminated widely across the NHS via the Central Alerting System (CAS as described in our written response, Annex A, page 124).

7.3 *…that therefore deaths/serious injury reports arising from off label usage are being categorised properly?*

The data provided relates to what was reported to us. The free text submitted by the public and healthcare professionals is analysed and coded/categorised accordingly by MHRA.

In the reports given previously, the information suggested an off-label event occurred but was not confirmed at this point. We do not alter the coding of the 'reported' event even if the findings later conclude off-label use did not occur or was not confirmed.

From about 3000 events associated with urognaecological mesh reported to the MHRA between 2010 and 2018 inclusive, we have not found any evidence of systematic off-label use, or off-label as the root cause of adverse events associated with the use of urogynaecological surgical mesh for the treatment of SUI or POP.

It should be noted, there may be a clinical reason why a healthcare professional has no option but to use a device off-label in order to treat a patient. In our guidance we provide advice in such circumstances.

8. *Two of the reported events (one pre 2015 and one post) are classified as non-reportable (from manufacturer to MHRA) because of the occurrence of 'expected foreseeable side effects'. But as you say these side effects are listed in the manufacturer's instructions for use which presumably do not apply in these cases – indeed, that is why they are being reported under the 'off-label' category. Will these be followed up with the manufacturers?*

The reports described in our earlier response suggested off-label use and described complications such as pain and infection. These reports were sent to the manufacturer. It is the complications that were considered by the manufacturer to be 'expected foreseeable side effects' which is not normally reportable under the vigilance system. It still forms part of the post market surveillance requirements of a manufacturer to follow their devices in use and these types of reports feed into their quality and risk management systems. Equally, off-label use is generally considered non-reportable but should also be handled as appropriate by the regulatory authorities and the healthcare facility. Therefore, we issued guidance to raise awareness of what off-label use means, implications and advice to the NHS. We continue to keep this under review.

NHS
National Institute for Health Research

NIHR Response to the Call for Evidence for the Independent Medicines and Medical Devices Safety Review:

Background:

The National Institute for Health Research (NIHR) is the nation's largest funder of health and care research. The NIHR was established in 2006 under the government's health research strategy, *Best Research for Best Health*. The NIHR is primarily funded by the Department of Health and Social Care (DHSC) but also receives UK aid funding to support research for people in low-and middle-income countries. The NIHR works in partnership with the NHS, universities, local government, other research funders, patients and the public, to deliver and enable world-class research that transforms people's lives, promotes economic growth and advances science.

Governance:

The NIHR's work is directed by the Science, Research & Evidence Directorate at the DHSC working in partnership with directors of seven coordinating centres.

NIHR has developed an internationally-recognised model to ensure that our research answers the most important questions and is appropriately designed, efficiently delivered, unbiased, published in full, appropriately disseminated, and usable.

NIHR Partnerships:

NIHR invests over £1 billion annually to fund translational, clinical and applied health research spanning the whole innovation pathway. Together with the Medical Research Council which supports basic/discovery science, and research charities and the life science industry, the NIHR helps make the UK among the best places in the world to develop and launch innovative medicines, technologies and diagnostics.

Life science companies can access NIHR resources at any stage in their clinical development process and the Department ensures all parts of the NIHR are open to collaboration with Industry. The reputation and value of the NIHR to the Life Sciences Industry is highlighted in the Life Sciences Industrial Strategy and the Accelerated Access Review.

The NIHR provides the best possible environment for collaboration between the life sciences industry, charities, academia and the NHS. It supports, facilitates and enables life sciences industry collaborative and contract research, across the translational pathway from early translational (experimental medicine) research, through clinical research, to applied health research.

NIHR Translational Research Partnerships provide an internationally unique approach to early and exploratory drug development, providing ready-formed networks of leading universities and NHS hospitals set up to work with the life sciences industry to conduct translational research and tackle experimental medicine challenges in selected therapeutic themes. These initiatives to bring together the expertise in NIHR Centres and Facilities, maximising the offer to industry in key priority areas including dementia, cardiovascular

disease, joint and related inflammatory diseases, inflammatory respiratory disease, diet and lifestyle, and mental health.

The NIHR Clinical Research Network (CRN) supports the delivery of clinical research trials and other studies in the NHS to quality, time and target, providing world-class health service infrastructure (e.g. research support staff such as clinical research nurses; and research support services such as pharmacy, pathology and radiology) to support clinical research in the NHS in England.

Relevant NIHR Funded Research:

The following tables provide details of studies that have been funded or are currently being funded by NIHR relevant to IMMDS. The NIHR Journals Library, a publicly available resource contains full details of all NIHR-funded studies – including those listed here.

Surgical Mesh:

Programme	Title	Status	CI + Contractor
Health Technology Assessment	Clinical and cost-effectiveness of surgical options for the management of anterior and/or posterior vaginal wall prolapse: two randomised controlled trials within a Comprehensive Cohort Study	Current	Dr Fiona Reid, University of Aberdeen
Health Technology Assessment	Vault or Uterine prolapse surgery Evaluation two parallel randomised controlled trials of surgical options for upper compartment (uterine or vault) pelvic organ prolapse (VUE)	Current	Dr Christine Hemming, University of Aberdeen
Health Technology Assessment	Cerclage Suture Type for an Insufficient Cervix and its effect on Health outcomes (C-STICH)	Current	Mr Philip Toozs-Hobson, Birmingham Women's NHS Foundation Trust
Health Technology Assessment	Proper Understanding of Recurrent Stress Urinary Incontinence Treatment in women (PURSUIT)	Current	Professor Marcus Drake, North Bristol NHS Trust
Health Technology Assessment	Adjustable Anchored Single-Incision Mini-Slings Versus Standard Tension-Free Mid-Urethral Slings in the Surgical Management of Female Stress Urinary Incontinence; A Pragmatic Multicentre Non–Inferiority Randomised Controlled Trial: The SIMS Trial.	Current	University of Aberdeen
Health Technology Assessment	Male synthetic sling versus Artificial urinary Sphincter Trial for men with urodynamic stress incontinence after prostate surgery: Evaluation by Randomised controlled trial (MASTER).	Current	Professor Paul Abrams, North Bristol NHS Trust
Health Services & Delivery Research	Surgical Care for female urinary incontinence in England	Waiting to publish	Professor Jan van der Meulen, London School of Hygiene and Tropical Medicine
Health Technology Assessment	The Effectiveness and cost-effectiveness of Surgical Treatments for womEn with stRess urinary incontinence: An evidence synthesis (ESTER)	Complete	Professor Dawn Craig, University of Newcastle upon Tyne
Biomedical Research Centre	Safety and efficacy of low elasticity polyvinylidene fluoride (DynaMesh®-SIS soft) retropubic tension free midurethral sling in the treatment of stress urinary incontinence in women.	Complete	NIHR Cambridge Biomedical Research Centre

Health Technology Assessment	Clinical effectiveness and cost-effectiveness of surgical options for the management of anterior and/or posterior vaginal wall prolapse: two randomised controlled trials within a comprehensive cohort study results from the PROSPECT Study	Complete	University of Aberdeen
Biomedical Research Centre	*Effective haemostasis using self-expandable covered mesh-metal oesophageal stents versus standard endoscopic therapy in the emergency treatment of oesophageal variceal haemorrhage: A multicentre, open, prospective, randomised, controlled study.	Complete	NIHR University College London Hospitals Biomedical Research Centre
Healthcare Technology Co-operative	*SMART (Stapled Mesh stomA Reinforcement Technique)	Complete	NIHR Enteric Healthcare Technology Co-operative
Health Technology Assessment	UK Cohort study to Investigate the prevention of Parastomal Hernia (CIPHER)	Current	Royal Devon & Exeter NHS Foundation Trust

*** NB: These are studies which investigating the use of surgical mesh/tape for treatment of other conditions**.

Sodium Valproate:

Programme	Title	Status	Contractor
Efficacy and Evaluation Programme	Sodium Valproate for Epigenetic Reprogramming in the Management of High Risk Oral Epithelial Dysplasia	ongoing	University of Liverpool

How NIHR ensures that trials are compliant with the Pregnancy Prevention Plan:

The responsibility for compliance with regulation and ensuring trials and studies are conducted appropriately lies first and foremost with the sponsor of the work. The sponsor features on the published protocol and is the contracted organisation, which can be found on the NIHR funding and awards page of our website: https://fundingawards.nihr.ac.uk/search. The sponsor is usually the contracting organisation which hosts the Chief Investigator.

However the NIHR through its review and monitoring processes, has various points at which the need for compliance with regulation would be pointed out: First to applicants during the review process; then during contracting when evidence of compliance with regulation is needed (depending on the trial). This includes the requirement to provide evidence of ethics approval including the approval number. Trial registration and evidence of that is also required. In addition, the protocol of a study or trial is published on the NIHR's website. Therefore it is at each of these points, when applicable, the issue of compliance with the Pregnancy Prevention Programme would be reviewed.

General Pharmaceutical Council

Shared a new video which has been send to all registrants in their e-newsletter: *Supplying Sodium valproate safety to women and girls*

UK Teratology Information Service

We note the wide range of communications available from your website. Please can you detail any other mechanisms you have used for communicating your knowledge of teratogens to:

a) Patients

Other organisations promote our services and our leaflets in their literature and on websites including nhs.uk. We have accounts on social media which we use to advertise our patient information leaflets, including those we have on known teratogens. We write articles for publications/magazines, and we have pharmacists who work in the community that direct patients to our online information.

b) Healthcare practitioners

We provide risk assessments to healthcare providers who telephone our national service for advice regarding drug and chemical exposures in pregnancy. The majority of our enquiries are risk assessments regarding women who have been exposed to medication in pregnancy but we also frequently provide pre conception counselling, risk assessments regarding paternal exposure and information following occupational and environmental exposures in pregnancy.

HCPs can access approximately 350 individual systematic reviews of the literature which are detailed, fully referenced, clinically focused scientific monographs on drug and chemical use in pregnancy. These are freely available to NHS HCP's via www.TOXBASE.org (subscription required) and summaries of the full documents are openly accessible to everyone on www.uktis.org.

We are commissioned by PHE to routinely collect pregnancy outcome data following exposures in pregnancy as part of ongoing national surveillance, UKTIS data collection and processing is covered by section 251 of the National Health Service Act 2006 and Regulation 3 of The Health Service (Control of Patient Information) Regulations 2002 (Public Health England Approval Reference Number: 13091).

We regularly publish and present prospectively collected pregnancy outcome data and we also collaborate with other teratology services around the world to publish findings in the field of teratology. We provide lectures and talks to various groups/courses/conferences on the safety of medications in pregnancy. We have in the past also paid for or offered stands to advertise our services at conferences for GPs, Midwifes, Pharmacists and Fetal Medicine specialists. Our services are promoted to HCPs by organisations including the RCOG, individual NHS Hospital Trusts, ENTIS, NICE, CSK, UKMI. Information about the availability of particular leaflets is regularly incorporated into NICE Clinical Knowledge Summaries, which are widely used within primary care in the UK.

c) Regulators

We regularly attend national meetings and consortiums regarding medication use in pregnancy. We are also involved in collaborations with other organisations and bodies where regulators are often stakeholders.

We would welcome any suggestions you have for running a registry on the impact of in utero exposure to anti-epileptics, in particular:

a) How should participants be recruited to the register?

Are you asking what method of promotion should be used or what method of data collection should be used?

Promotion - We are just about to lead a task to promote PV systems routinely collecting drug exposure in pregnancy and outcome data as part of IMI ConcePTION. Previously we were involved in IMI PROTECT where promotion outside of clinical settings wasn't very successful. We used various methods to direct women to an online reporting system but recruitment was poor. We published the findings which can be accessed here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4869218/.

Data collection - An effective method of obtaining the most complete dataset is to speak to women face to face, this was the preferred method that women chose in a small sample of patients we asked in a local fetal medicine unit, however, this is time consuming and expensive. Another option and one used very successfully by Lew Holmes and his team at the North America Epilepsy Registry and by the UK Epilepsy Pregnancy Register is to collect data by telephone.

As you know we have an online reporting system (***BUMPS***) which we are using to collect data for trials and it is also open for spontaneous reporting. Online reporting is certainly a cheaper option but I'm not sure how successful it is when compared against telephone and F2F data collection. Having more than one data collection method would be preferable.

Although the question you ask only relates to the registration of participants, how will you collect the pregnancy outcome data? Getting women to complete questionnaires after their pregnancy has ended can be difficult. Do you intend to collect data from HCPs also?

b) How long should individuals be followed up for?

Ideally until adulthood, if you want to monitor neurodevelopment. We would defer this question to Rebecca Bromley. Our online reporting system (***BUMPS***) was designed to collect data up until the age of 16.

c) What details should be included on the register?

This depends on what you are looking to use the data for. Our bespoke pregnancy exposure database captures information taken from HCPs and has over 200 data fields. I think the BUMPS record for pregnant women has substantially more fields. It is important to collect detailed information about both biological parents to be able to rule out potential confounders when assessing congenital malformation risk.

What is the uptake of your Bumps Online services? How many Bumps personal records were created last year?

Approximately 400 records were created in the last financial year. We don't actively promote the ***BUMPS*** record as we don't have the funding available to do this. We rely on women coming to the website for information on drug use in pregnancy and signing up to report their pregnancy whilst they are there.

How often were your leaflets downloaded or viewed? (If you have a breakdown by leaflet that would be very helpful)

The patient information leaflets available via www.medicinesinpregnancy.org were accessed over 2 million times in the last financial year, 2018/2019, roughly 5,800 accesses per day.

We don't routinely download data for all the leaflets, but here is a list of our top 20 accessed leaflets in the first quarter of 2019/2020. As you can see they move up and down the ranking over time.

Rank	Leaflet Name	Hits in Q1.2019-20	Rank in Q4.2018-19
1	Constipation	14,671	1
2	N&V	11,801	6
3	Clotrimazole	11,563	4
4	Sertraline	10,659	2
5	Threadworms	10,177	5
6	Paracetamol	9,825	3
7	Omeprazole	9,318	8
8	Cetirizine	9,134	13
9	Codeine	9,066	7
10	Penicillins	8,309	11
11	Loratadine	8,161	12
12	Aspirin	7,246	17
13	Amitriptyline	7,021	9
14	Metronidazole	7,014	10
15	Citalopram	6,478	14
16	Ibuprofen	5,914	15
17	Chlorphenamine	5,540	22

18	Lamotrigine	5,210	20
19	Essential oils	5,087	16
20	Fluoxetine	4,988	18

We certainly have the infrastructure to help with data collection if that would be helpful. We have a national telephone line which is open during office hours which could be utilised to collect information from patients or their HCPs. In addition, at the time of the call we would also be able to provide risk assessments and information to HCPs about their patients if required. We are not commissioned to provide counselling for women via the telephone (we can only do so via their HCPs) but we could collect information from them and point them in the right direction to access more advice and/or engage with their prescriber/HCP.

We have a bespoke database which we use to record all our pregnancy data. Outcome data is collected via a questionnaire via an automated system on the database. Data is easily extracted and downloaded as a CSV file. We would be able to pass all AED data on that we collect via the service for analysis if required. Because we collect data on all pregnancy exposures we also have information on individuals that can be used as control data for analysis.

Participants could also be asked to register to the ***BUMPS*** website. Our ***BUMPS*** record has the ability to collect online data until the pregnancy ends. The system has been designed to allow all women who report a liveborn infant to be reminded annually, by email, to log in and complete a short questionnaire about their child's health and development.

In summary, UKTIS has the ability and infrastructure to manage a registry on antiepileptic drugs and pregnancy. We have an existing database, dedicated phone line and well established mechanisms for analysing and reporting this type of data. However, we would require help with regard to promotion of such a registry and on-going resources to encourage healthcare professionals and patients to input data. Work should be undertaken to facilitate linkage of data from other sources (e.g. the Maternity Services Data Set, NCARDRS) since outcome data can then be automatically collected and cross-referenced with reported data from HCP and patients. Promoting a culture of reporting cases to the registry and minimising missing outcome data (through automatic data collection) is essential in order to accurately capture the effects of AEDs in pregnancy.

The Independent
MEDICINES & MEDICAL DEVICES
Safety Review

Request for information sent to Clinical Leads for the named units designated to treat women with mesh related problems.

Dear

As you will be aware, in February this year the former Secretary of State for Health, the Rt Hon. Jeremy Hunt MP, announced a review into the how the healthcare system in England responds to reports from patient about the harmful side effects from medicines and medical devices. That announcement followed patient-led campaigns on the use of the hormone pregnancy test Primodos, the antiepileptic drug sodium valproate for women and girls of child bearing age and pelvic mesh. The Review is chaired by Baroness Julia Cumberlege.

The Independent Medicines and Medical Devices Safety Review, which has been listening to the personal testimonies of those patients and families directly affected by one of the three interventions in a series of country wide engagement events, is now in its Call for Evidence phase addressed not only to the representative patient groups but also to the manufacturers, clinicians, regulators, NHS and other health care providers and other public bodies. The Review's oral hearing sessions will follow shortly after the close of the Call for Evidence and will run through to the spring of 2019.

You can read the Review's Terms of Reference and about the Review's process protocols on our website at www.immdsreview.org.uk

As part of the Review's evidence gathering in relation to pelvic mesh I am writing to you now, as the clinical lead for one of the named units designated to treat women with mesh related problems, for your assistance in answering the following questions:

i) 10 year data split by year for all types of SUI and prolapse surgery, including removals and pelvic mesh related surgery, by procedure type;

ii) Please detail the size of unit and composition by profession;

iii) What are your current waiting times? Is your unit working at capacity or could your unit undertake more procedures? If so how many more could they undertake?

iv) Geographically where do your patients come from?

v) Please provide your mesh removals numbers and if known where the insertion occurred (own hospital, other NHS, Private);

vi) Please can you provide a breakdown of mesh removal surgery by
- type of mesh
- reasons for removal, e.g. pain, infection, ineffective device, etc;

vii) Do you refuse to undertake mesh removal surgery in some patients? If so on what basis and what proportion of cases? What happens to these patients?

viii) What proportion/number of the procedures you undertake are reported on the BSUG database?

ix) Please provide any Yellow card reports by year for mesh related procedures;

x) There is a current Consultation on specialist commissioning,[1] do you feel your unit meets the standards set by the Specialist Commission consultation?

xi) Please specify the criteria used to certify as a specialist centre?

I should be grateful to receive your response, addressed to me at reviewteam@kcl.ac.uk, no later than **Friday 16th November 2018.**

Your written response will be considered as evidence to the Review and will be posted on our website in accordance with the Review's information handling policies.

Thanking you in advance for your co-operation,

Yours Sincerely

Valerie Brasse
Review Secretary

[1] https://www.engage.england.nhs.uk/consultation/gynaecology-surgery-and-complex-urogynecology/user_uploads/complications-of-vaginal-mesh-draft-service-specification.pdf

Specialist Mesh Centres evidence summary

Of the 26 specialist mesh centres contacted as part of our call for evidence, 17 responded with evidence in the form of replies to a series of targeted questions. The units have been anonymised and will be referred to as 'Trust A', 'Trust B' etc. The questions posed by the Review, and a summary of responses, are laid out below.

i) 10 year data split by year for all types of SUI and prolapse surgery, including removals and pelvic mesh related surgery, by procedure type

A summary of the data provided by the trusts appears in table 1 below - including the number of trusts reporting a particular mesh procedure, as well as the mean and range for reported numbers for each year.

Procedure	No. trusts offering procedure		2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Colposuspension	11	Mean	2.8	1.9	2.4	4.0	3.4	3.6	4.2	5.6	4.0	9.0	12.0
		Range	0-14	0-9	0-14	0-24	0-15	0-13	0-19	0-22	0-19	0-19	2-24
TVT	13	Mean	76.5	73.8	83.8	82.7	80.2	93.2	76.7	63.6	47.2	40.7	14.9
		Range	0-211	0-175	11-162	18-169	20-182	10-225	7-133	15-108	12-99	7-87	0-41
TOT/TVTO	9	Mean	19.7	25.6	28.0	32.0	38.9	47.1	31.6	31.3	22.8	21.9	13.9
		Range	0-110	0-114	0-113	1-130	1-136	1-184	2-75	0-101	0-85	0-112	0-93
Bulking agent injection	9	Mean	11.4	10.7	11.0	10.7	15.7	11.9	14.1	17.6	14.6	21.3	15.6
		Range	0-48	0-35	0-31	1-30	1-76	1-54	2-74	0-93	0-81	2-61	3-36
Full TVT removal	8	Mean	4.2	5.2	4.4	5.4	8.2	6.0	5.4	9.0	9.0	13.8	24.3
		Range	0-9	0-15	1-9	1-11	1-20	0-14	0-11	0-17	1-32	1-47	0-63
Partial TVT removal	10	Mean	2.5	2.0	4.5	5.5	4.3	5.3	4.0	3.3	3.2	4.2	5.2
		Range	0-6	0-4	0-8	2-10	1-7	0-11	2-6	1-8	1-8	2-8	1-10
TOT/TVTO removal	6	Mean	1.4	2.8	1.9	3.4	3.9	3.1	2.9	4.5	5.1	7.8	10.3
		Range	0-9	0-15	0-6	0-11	0-20	0-14	0-11	0-17	0-32	0-47	0-63
Sacrocolpopexy	11	Mean	9.8	10.5	15.7	14.2	11.5	21.2	20.4	21.8	18.5	18.7	11.4
		Range	0-28	0-31	2-53	2-46	1-33	1-60	1-82	3-56	3-37	1-61	1-37
Sacrospinous fixation	10	Mean	12.6	12.3	17.9	21.3	18.7	22.9	24.0	25.0	25.6	26.8	23.1
		Range	0-55	0-53	1-93	1-132	0-106	1-134	0-120	0-131	2-124	3-112	1-99
Sacrohysteropexy	5	Mean	1.0	1.8	6.3	13.5	14.5	38.3	52.3	41.5	34.0	38.6	22.6
		Range	0-3	0-6	0-25	0-44	0-46	1-126	0-178	1-145	0-148	0-178	0-107
Anterior repair	7	Mean	70.4	68.4	71.6	70.1	71.6	76.7	70.7	79.0	70.1	77.4	53.0
		Range	0-139	0-124	22-112	6-118	10-120	12-157	3-116	3-129	6-121	7-133	4-111
Posterior repair	7	Mean	35.3	35.5	39.3	36.2	39.8	51.2	49.8	56.0	56.8	52.0	38.2
		Range	0-87	0-84	9-93	12-92	0-92	0-113	0-102	1-109	0-128	0-123	0-82
Manchester repair	5	Mean	3.8	4.6	5.0	3.8	4.4	9.4	5.4	2.0	2.0	2.8	2.8
		Range	0-9	0-14	0-19	0-17	0-13	0-27	0-22	0-5	0-7	0-4	1-5

Table 1: A table showing a summary of procedures reported by the specialised mesh units, as well as how many units reported a given procedure. Mean and range values are given for each procedure in a given year.

Table 1 contains only data for respondents that provided a partial or full 10 year breakdown of the data covering a consistent range of procedures. Four of the seventeen responses were disregarded; One response was excluded as it provided only removal numbers (not differentiated between full or partial) another gave data that spanned the entire 10 year period but was only for removals (again, not differentiated between full/partial) another gave rough estimate values, not broken down by year and the last responded that "we do not have this information available"

Please detail the size of unit and composition by profession.

Table 2 summarises the constituent professionals detailed by the specialist mesh units. It gives the number of units reporting a professional, as well as a mean and range value for each professional.

		Number of each profession	
Profession	**Units reporting involvement of a given profession**	**Mean**	**Range**
(Consultant) Urogynaecologist	16	3.4	2-10
Specialist Nurse	16	3.4	1-8
(Consultant) Urologist	14	3.1	1-18
Physiotherapist	13	2.0	1-5
(Consultant) Colorectal Surgeon	12	1.9	1-6
(Consultant) Pain Specialist	9	1.9	1-3
(Consultant) Radiologist	8	2.0	1-3
Clinical (Research) Fellow	4	2.0	1-3
Subspeciality Trainee	3	2.0	1-3
Clinical Scientist	3	2.0	1-3
Healthcare Assistant	2	2.0	1-3
Secretary	2	1.5	1-2
Anaesthetist	2	1.0	N/A
Continence Nurse Consultant	2	1.0	N/A
Geriatric Consultant	1	1.0	N/A
Midwife	1	1.0	N/A
Plastic Surgeon	1	1.0	N/A
Medical Physicist	1	1.0	N/A
Lead Nurse	1	1.0	N/A
Obstetrician	1	12.0	N/A
Urology/gynaecology specialist registrar	1	3.0	N/A
Community Continence Advisors	1	11.0	N/A

Table 2: A table showing the professions detailed by the specialist mesh units as being part of the unit. The number of units mentioning at least one of a given profession is shown, as well as mean values and a range for the number of a given profession reported. 'N/A' denotes no range, due to there being only one report.

iii) What are your current waiting times? Is your unit working at capacity or could your unit undertake more procedures? If so how many more could they undertake?

Trust A:

New patients - 3 months

Follow up - 2-4 months

Lab urodynamics - 3 weeks

Videourodynamics – 8 weeks

Outpatient cystoscopy +/- botox - 4-6 weeks

Unit currently working to capacity

Trust B:

The unit was unable to isolate out and provide specific waiting times for mesh. For the urogynaecology service as a whole, in September 2018, 58 out of 111 patients (52%) were treated within 18 weeks. In October, 76 out of 129 patients (59%) were treated within 18 weeks.

Trust C:

The trust mentioned that patients are seen on a standard pathway as per trust guidelines. It was noted that the unit is not working at capacity at present for mesh problems, and can take more.

Trust D:

The trust reports it follows an 18 week pathway and aims to treat patients within the agreed time. Due to the complex pathway with some mesh-affected patients, the diagnostic pathway can occasionally be longer. Further referrals could be accommodated if required.

Trust E:

The trust notes that waiting times vary somewhat between the Urology and the Urogynae Consultants. In Urology the wait for elective SUI surgery is approximately three to six months. For elective patients for SUI or prolapse, under Urogynae the average wait is twelve weeks.

Simpler mesh cases wait a similar time but complex ones requiring multi-speciality operating may wait longer due to the difficulty in co-ordinating the timetables of the surgeons involved.

The trust is working to capacity within Urology. Urogynae may have some spare capacity and would be willing to accept more cases.

Trust F:

It is noted that current waiting times for new referrals are between 3-6 weeks. All diagnostics are performed within 6 weeks. Ambulatory and day surgery procedures are completed within the 18

week wait pathway. For inpatients, main theatre lists waiting times are up to 40 weeks. Capacity has been increased to undertake more diagnostics, ambulatory and day care procedures but access to inpatient beds and main theatre operating lists is limited.

Trust G:

It is noted that waiting times are approximately 3 months for surgery.

Trust H:

The trust notes that it mostly operates within the 18 week framework. Potential mesh complications are operated on urgently. There is no spare capacity.

Trust I:

The trust currently complies with 18 week pathways. Due to the 'pause' on suburethral tapes, the unit is receiving an increased number of referrals for SUI procedures from other regional units that are currently unable to offer alternative SUI procedures. The system has coped to date but as referrals continue at the current level, delays at all points in the pathway have begun to occur. Extra resources would be required to further increase capacity.

Trust J:

Current elective waiting times for outpatients are 20 weeks and 6 month waiting time for surgery. The Unit is working at capacity. The Trust recognises that Urogynaecology referrals are increasing, complexity is also increasing and there is a recognition that the infrastructure will need to expand to accommodate this. At the time of response, the trust had 72 patients in Gynaecology waiting over 52 weeks - reducing through a number of initiatives.

Trust K:

The trust notes that it is compliant with the NHS waiting times 18 week RTT standard.

Trust L:

The unit notes that it has the potential to undertake more procedures (provided that it is appropriately commissioned and funded).

2018 Waiting times for out-patient clinics are as follows:

Urogynaecology – 7 weeks
Functional Urology – 8 weeks
Complex Urogynae (Mesh Clinic) – 6 weeks
Colorectal Surgery – 4 weeks
Joint Urogynaecology – Colorectal – 4 weeks
Urodynamics – 3 weeks
MDT Review – 1 week
Virtual Clinic (On-line Questionnaire + Telephone Consultation) – 4 weeks

2018 Waiting times for surgery are as follows:

Urogynaecology – 3 months
Functional Urology – 3 months
Colorectal Surgery – 1 month
Outpatient procedures (Diagnostic & operative cystourethroscopy) – 2 months

Trust M:

Current waiting times for routine appointments/ diagnostic tests and to surgery if needed:

8 weeks for first appointment

6 weeks for diagnostics

6 weeks for procedures

It is noted that there would be capacity to undertake more mesh specific work. 5-8 cases per month.

Trust N:

Currently, in Urogynaecology, the average waiting time for new referrals to be seen is 8 weeks. All patients for Urodynamics receive their diagnostic tests within 6 weeks. Most follow up appointments are being arranged in time, with some patients' appointments overdue by up to 3 weeks. In the current waiting list for surgery, the longest any patient has waited from referral to surgery is 17 weeks, which is within the 18 week pathway. Nearly 50% of the patients are getting a date for surgery within 5 weeks.

The unit expects to be able to accommodate more patients with complex / recurrent incontinence and prolapse.

In Urology, patients are waiting 3-4 months for procedures for stress Urinary Incontinence.

Trust O:

Current waiting times vary according to consultant and range from 8 weeks to 16 weeks. All patients are pre-investigated, discussed at an MDT and channelled to the most appropriate consultant with the least waiting time. The unit reports that it is not currently at capacity and can take more referrals.

Trust P:

Current clinic waiting times are running at 8-10 weeks, however, the wait for surgery is approximately 36-40 weeks. The unit is currently working above capacity.

Trust Q:

The waiting time for incontinence services is 8-10 weeks, but 4-6 weeks for mesh salvage cases / referrals seen urgently. The unit would be able to accommodate more patients within the two directorates urology and gynaecology.

iv) Geographically where do your patients come from?

Eight of the trusts noted referrals from centres within the surrounding area, six noted referrals from the immediate area with tertiary referrals from further afield. Three trusts noted referrals from CCGs spanning the country.

v) Please provide your mesh removals numbers and if known where the insertion occurred (own hospital, other NHS, Private)

All centres responded to this question. Three directed attention to their responses to the first question, as mesh removal numbers were given in response to this. One trust remarked that it did not have accurate information as mesh removals had only just started to be entered onto the BSUG database.

Twelve centres gave data on mesh removals and of these, seven provided data about the site of mesh insertion.

Of those providing mesh removal numbers, one provided a 10 year breakdown, one provided a breakdown between the years 2016-2018, another from 2012-2018. Six centres provided total numbers of mesh removals over the 10 year period 2008-2018. These centres performed between 30 and 118 mesh removals in this time, with a mean removal number of 65. One trust provided total numbers of removals for the 3 year period 2015-2018 (31 mesh removal surgeries performed in this time). One trust provided total numbers of removals between 2009 and 2018 (196 mesh removal surgeries performed in this time).

Of the seven centres providing data on site of mesh insertion, one provided a breakdown from 2012-2018 and another from 2016-2018. The remaining five centres provided 10 year total data.

Proportions of total mesh removals from different insertion sites (own trust, other NHS trust, private practice) are summarised in table 3 for those that provided this breakdown.

	Site of mesh insertion (%)		
Reporting Trust	**Own Trust**	**Other NHS Trust**	**Private**
B	36.3	60.0	3.2
D	4.8	95.2	
F	34.3	57.8	
H	80.0	20.0	
I	45.0	50.0	5.0
L	43.9	46.3	9.8
N	88.9	11.1	0.0

Table 3: A table summarising the proportions of removed meshes inserted at the same trust, another NHS trust, or within the private sector. Where values for 'other NHS trust' and 'private' are merged, this is because these were not differentiated in the response.

vi) Please can you provide a breakdown of mesh removal surgery by type of mesh and reasons for removal e.g. pain, infection, ineffective device, etc.

One trust gave summary data for mesh removals - alongside clinical indications - performed between 01/01/09 and 11/12/18, summarised in table 4.

Procedure	Number of cases	Indications
Laparoscopic removal of Sacrocolpopexy mesh	7	Recurrent vaginal mesh erosion, pain
Laparoscopic removal of hysteropexy mesh	5	Pain, vaginal mesh erosion in two cases
Excision vaginal part of MUT (exposed or not exposed)	34	Pain, vaginal mesh exposure
Posterior IVS Mesh removal	1	Pain, vaginal mesh erosion
Laparoscopic and vaginal Uphold mesh removal	1	Pain, vaginal mesh erosion
Laparoscopic TVT removal from the bladder	6	Bladder mesh erosion
Localised excision and closure of vaginal mesh	5	Vaginal mesh exposure
Mesh Erosion (vaginal suburethral) – excised	17	Vaginal mesh erosion
Total excision of vaginal wall mesh	7	Pain, mesh erosion
Total removal of retropubic tape – laparoscopic	106	Pain at multiple sites
Removal of transobturator tape	4	Pain, vaginal mesh erosion, groin abscess
Urethral mesh removal	3	Urethral mesh erosion

Table 4: A table summarising mesh removal data for a particular specialised mesh centre - as well as their respective clinical indications – for the period 01/01/09 – 11/12/18

Another trust gave a yearly breakdown of mesh removals from 2008 to 2017, with some indication of reasons for removal, summarised in table 5.

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Eroded TVT removal	0	2	2	2	1		1	2	2	3
TVT excision (pain)	3	2	3	1	1	1	2	1	1	1
TVT stretch	2	0	4	1	2	6	3	1	3	0
Tape division	0	2	3	3	0	2	5	1	1	0
TOT removal (pain)	0	0	0	1	0	0	1	0	0	0
Mesh removal due to vesicovaginal fistula	n/a	n/a	n/a	0	1	0	0	0	0	0

Table 5: A table summarising mesh removal data for a particular specialised mesh centre – with some limited indication of reason for removal – from 2008-2017

Four trusts did not provide data. One commented that procedures were predominantly midurethral tape removals/partial excisions. Another trust remarked that often, they do not know which types of mesh are inserted elsewhere and had not been collecting this data prospectively until recently. The third commented that they had collected data for removal procedures within the urology department but not urogynaecology, combined with poor coding, this was likely to lead to inaccurate numbers. The trust did, however estimate a mesh removal rate of 5 per year on average, acknowledging more removals in the last 5 years than previously.

One trust cited incomplete data and poor coding, resulting on no mesh removal cases being recorded. An internal audit was provided, which included all MUS insertions between 01/01/2010 and 31/12/2014 (661 TOTs and 263 TVTs). 13.7% had a further procedure at a mean time of 22 months after initial surgery. 9.5% of TOT patients and 3% of TVT patients required additional surgery, with 2.8% of all women receiving a TVT or TOT undergoing a shortening, reburying, or excision of the vaginal portion of their mesh.

The remaining 10 centres provided total removal numbers from the period 2008-2018. Two gave estimated proportions of removal procedures (summarised in table 6) and the remainder provided removal numbers, which are summarised in table 7.

	Proportion of removals (%)	
Removal procedure	**Trust L**	**Trust I**
TVT	30	80
TOT	30	10
Vaginal prolapse mesh	10	
Abdominal prolapse mesh	15	
Abdominal rectopexy mesh	15	
Other mesh		10

Table 6: A table summarising the estimated proportions reported by two specialised mesh units of different mesh removal procedures, during the 10 year period 2008-2018.

		Removal Numbers	
Removal Procedure	**Number of centres reporting**	**Mean**	**Range**
MUS/T	3	21	5-45
Vaginal prolapse mesh	3	20	4-34
Abdominal prolapse mesh	3	18	1-51
Sacrocolpopexy mesh	2	5	3-7
Sacrohysteropexy mesh	1	7	N/A
Prolapse mesh	1	16	N/A
Incontinence mesh	1	98	N/A
Abdominal prolapse and incontinence mesh	1	1	N/A
TVT	5	21	3-47
TVTO	2	5	1-8
TOT	4	14	1-25
TVT/TOT	1	46	N/A
Mini-Arc	1	5	N/A
Macroplastique	1	7	N/A
Unknown MUS	1	4	N/A
Other tapes	1	3	N/A

Table 7: A table summarising the data provided by the specialised mesh centres that provided total values for mesh removal procedures over the 10 year period 2008-2018. Included is the number of centres reporting a given mesh removal procedure, as well as the mean number of removals being performed, and a range.

Seven centres did not provide data about the reasons for mesh removal. One centre cited a lack of clinical detail on their database, another cited under-reporting and poor coding. A third provided no

data but did state that the majority of removals have been for pain or recurrent exposure. Only a small proportion have been for infection/abscess. Another centre gave no data but indicated that the majority of patients had surgery for voiding dysfunction, pain, bleeding and mesh exposure. Another indicated that they did not have this information and another simply provided no data. The unit that provided a five year audit did not include clinical indication for mesh removals.

One centre referenced an internal retrospective review of all women presented to their unit with mesh complications from January 2012 to September 2018. Of the 62 patients, 16 were due to urethral erosion, 7 resulting from bladder erosion, 24 from vaginal extrusion, 12 due to voiding dysfunction and 3 pain.

The remaining centres provided data summaries covering the period 2008-2018. The data provided by five centres as raw numbers of clinical indications is compiled and summarised in table 8. Two centres provided proportions of mesh removals resulting from different clinical indications, these are summarised in table 9.

Reason for removal	Number of centres reporting	Mean	Range
Erosion (bladder/urethra/rectum)	5	30	16-48
Infection	3	7	1-17
Vaginal exposure/extrusion	4	30	7-74
Pain	4	22	4-49
Recurrent UTI	2	11	5-17
Voiding difficulty	3	10	2-19
Fistula	1	1	n/a
Tightening	1	1	n/a
Dyspareunia	1	7	n/a
Urethral diverticulum	1	6	n/a
Incontinence	1	40	n/a
Other/unknown	1	1	n/a
Failure	1	18	n/a

Table 8: A table summarising the data provided for the total values of mesh removals due to a particular clinical indication (noted as 'Reason for removal') for the 10 year period 2008-2018. The number of centres reporting a mesh removal due to a particular clinical indication is give, alongside the mean number of mesh removals for this indication, and range.

	Proportion of mesh removals (%)	
Reason for removal	Trust I	Trust L
Pain	60	30
Erosion/exposure	30	60
Other	10	
Patient Request		10

Table 9: A table summarising the estimated proportions of mesh removal procedures due to a particular clinical indication (noted as 'Reason for removal') for the two trust that answered the question in this way.

vii) Do you refuse to undertake mesh removal surgery in some patients? If so on what basis and what proportion of cases? What happens to these patients?

Trust A:

The trust does, if the MDT, feels that the risks are greater than benefits. This happens in about 10% of patients. 1 patient has been referred to another centre. All options would be looked at.

Trust B:

The trust states that from experience, the women seen fall into several categories:

1) Those who have mesh perforating an organ (urethra, bladder or bowel) or evidence of infection
    a) In these cases the decision process is simple; they need surgical removal unless their other medical co-morbidities prohibit intervention.
2) Those with vaginal mesh exposure or extrusion, where organ perforation or infection has been excluded
    a) If asymptomatic they may wish to be monitored.
    b) If bothersome we would offer treatment which may involve removal of part or all of the mesh.
3) Those with voiding difficulties
    a) This may or may not require surgery.
    b) It may involve division or removal of the tape, depending of patient wishes, investigation findings and the presence of other symptoms.
4) Those with recurrent UTI, where urinary tract injury has been excluded
    a) High uncertainty about removal of mesh we would endeavour to treat the cause of the UTI.
5) Those with pain:
    a) Directly attributable to mesh insertion – spatial and temporal. We would discuss partial or complete mesh removal.
    b) If pain may be attributed to the mesh, the trust would first counsel, based on the experience from the Glasgow group, that only 50% may improve with removal. The trust completes a pain detect questionnaire and involve the pain team prior to surgery.
    c) If the pain appears to be completely unrelated and attributable to another aetiology then the patient would be advised on further referral.
    d) Some women have mild pain and primarily have symptoms relating to fear of the long-term consequences of polypropylene mesh and its impact on their immune system. The trust is unaware of any evidence of the long-term safety or harm of mesh. Surgical removal may help to alleviate anxiety but may cause harm with the risk of severe complications. Some of these women are reassured by ultrasound of their mesh sling or a normal cystourethroscopy and the offer of ongoing annual surveillance. However, the trust is aware that a small number will seek a clinician in the private sector to remove mesh.

Patients having mesh removal surgery are counselled that it may not be possible to remove all of the mesh. This particularly applies to vaginally inserted mesh “kits” and trans obturator mesh slings where there have been previous attempts at mesh removal before referral.

Trust C:

The trust does make such refusals on occasion, unless there is clear abnormality, there are no indications for removal. Patients who do not have removal will be seen by a pelvic floor consultant, biofeedback clinic and in appropriate cases in the pain clinic with psychological support if required.

Trust D:

The trust does refuse removals, but this is on an individual basis where it has been felt inappropriate to do so. Approximately three such cases have occurred, which have continued to be followed up in an MDT/pain setting

Trust E:

The trust is not aware of any refusals for any patient who has been seen who requires surgery. There have been no referrals outside of the trust.

Trust F:

Yes – if it is considered that mesh removal would lead to greater risks than benefits, women would be offered non-surgical management in the form of vaginal oestrogens, physiotherapy including appropriate adjuvant therapy e.g. dilators, massage etc, referral to pain clinic, psychosexual counselling and the possibility of steroid injections into the site of pain.

Trust G:

No. Some patients will still want removal of mesh despite normal investigations and minimal symptoms. These procedures have been undertaken if the patient wants to proceed even after detailed discussions.

Trust H:

Mesh removal is not refused if required. Patients that are beyond the skills of the trust are referred to another centre.

Trust I:

The unit does decline to remove tape if this is the MDT decision. All cases are considered on an individual basis and to include all factors. Additional opinions are sought where felt appropriate and patients counselled thoroughly throughout the process. Around 10-15% of patients are reassured when given explanations as to why the MDT does not think 'mesh' removal is in their best interests. Less than 5% of patients disagree with our decision and may seek an opinion from another centre

Trust J:

The trust does refuse to undertake mesh removal surgery in patients where it is felt that this will be of no benefit. Typically, this would be a patient with a variety of systemic symptoms, they may attribute this to mesh. Clinicians would discuss within the MDT, if it is felt that their symptoms are unlikely to be attributable to mesh, and risks of mesh removal exceed potential benefits, the patient would be advised accordingly. Some of these patients may subsequently seek a second opinion elsewhere, the majority however are reassured and accept the clinical advice.

Trust K:

The trust's pathway is to remain conservative with a step by step process. The trust injects local anaesthetic with depomedrone and removes mesh exposures prior to any discussion around total mesh removal.

Trust L:

No. All cases and all requests for removal are considered. The trust is happy to receive referrals and discuss the care of patients in other units, likewise it is happy to refer patients seen in the unit to other centres at patient request or when clinically indicated.

Trust M:

Mesh removal is only refused on clinical grounds or if deemed inappropriate by MDT discussion. Such patients would be offered another opinion at an alternative unit.

Trust N:

So far, the unit has not had to refuse mesh removal surgery to any patient. No patients have requested total removal of mesh after thorough assessment and counselling. In case there are cases like this in future, the trust may be able to offer this service within the multidisciplinary team working.

Trust O:

The unit performs removal surgery if there is an absolute indication (extrusion into urinary or GI tract), or it is necessary for ongoing treatment of SUI (i.e. before insertion of bladder neck artificial urinary sphincter if MUT is adversely affecting surgical access).

The unit offers removal surgery to patients with chronic pain who experience local pelvic and/or vaginal pain, provoked or persistent, where local mesh palpation generates or exacerbates pain symptoms, and where pain management interventions have been unsuccessful or are deemed inappropriate.

In patients who report pain symptoms in the absence of mesh tenderness, or where mesh palpation does not reproduce pain symptoms; surgical removal will be considered after MDT review and pain management involvement. In this group of patients, significant objective evidence of pain centralisation would militate against a recommendation for surgical removal. The unit does not offer surgical excision in patients who are well but concerned about the risk of future mesh complications, or patients who have systemic symptoms or disease attributed to mesh, in the absence of local complications that necessitate surgery. The unit may not offer removal to patients who are not fit for major surgery, or in those patients where there is an expectation that the morbidity of surgery would be greater than the symptoms attributed to mesh.

The unit refuses to undertake removal surgery in a small minority of patients, and a reasonable estimate would be around 5% of referrals for mesh-attributable complications. If the unit does not operate, these patients will have their symptoms palliated by clinicians within the MDT: (1) Pain Medicine (2) Urology (3) Urogynaecology (4) Colorectal, or by other specialties as appropriate. If a patient request for surgery is refused, the trust would always suggest that they seek a second opinion outside of the unit.

Trust P:

The trust has not had an incidence where the team has refused such surgery. A second opinion has been requested in a few unusual cases.

Trust Q:

The trust has not refused a patient this service, but had one patient that requested to be referred elsewhere.

viii) What proportion/number of the procedures you undertake are reported on the BSUG database?

Nine trusts state a 100% reporting rate to BSUG. One trust states a "close to 100%" reporting rate. One trust stated that 100% of mesh removal surgery performed by their gynaecology team members is entered onto the BSUG database. The mesh complication surgery performed by the urology team members has not been entered onto the BSUG database - as urologists they are not members of BSUG. The urological mesh removals have been entered on a separate urology FFR database.

One trust stated a 94% reporting rate in 2018. Another stated a 91% reporting rate in this year.

One trust stated a >90% reporting rate of urogynaecology procedures to BSUG.

One trust stated a >80% reporting rate. Another reported an 80% reporting rate.

One trust noted that it has not begun reporting to BSUG, although MHRA reporting is ongoing.

Two trusts noted that the BSUG database has only been updated in the last couple of years (since 2017) to allow more complex reporting of mesh complications.

ix) Please provide any Yellow card reports by year for mesh related procedures

All trusts except for one responded to this question. Responses were either given as a proportion of mesh related procedures reported to MHRA or as a number or reports submitted in 2018. Some trusts sent yellow card reports to us, others did not.

Of those providing a number of reports made, responses ranged from "at least 30" (timescale not given and unable to give exact numbers due to loss of emails from a change in email platforms) to "2 in 2018" and "6 for the period from 2015 to 06/03/18". One trust noted that whilst it was known that reports had been completed, it was unknown how many, and reports were not available.

Of those providing reporting proportions, five trusts noted a 100% reporting rate (either in 2018 or timescale not mentioned) and one mentioned a 91% reporting rate in 2018.

Of those providing reports, one trust provided 17, dated between 01/07/16 and 03/10/18 and another provided 12, dated between 03/10/17 and 01/03/18. One trust provided a single report as an example, commenting that Yellow card reports have been completed for some patients with mesh related complications at the trust, but not all.

One trust stated that it has incomplete data, with 2 consultants having email records of MHRA reporting, but this was not representative of the whole unit (no mention of number of reports or proportion of procedures reported by these consultants).

One trust noted that its urology department had not kept reports of mesh removals separately in an accessible file whilst the gynaecology department had kept a separate file of their reports. The trust resolved to "keep a file of all our MHRA reports from hence forth".

One trust noted that the criteria for reporting to the MHRA were not initially clearly defined and as a consequence there has been some variation in reporting.

One trust cited the lack of a direct link between the BSUG or BAUS website to the Yellow Card reporting platform as the reason for reduced reporting prior to 2018.

One trust was unable to send Yellow card reports due to the inclusion of patient identifiable data, stating that It would be useful going forward for the MHRA to supply each unit/surgeon with an anonymous annual report of their submissions.

x) There is a current Consultation on specialist commissioning, do you feel your unit meets the standards set by the Specialist Commission consultation?

The responses from individual trusts are given below:

Trust A:

The trust expressed that it does not meet the specialist commissioning standards due to the lack of a plastic surgeon and psychologist, although it is expressed that involvement of the two would not be difficult to arrange.

Trust B:

The trust expressed that its mesh service meets the majority of the standards set by the specialist commissioning consultation:
• All Urogynaecologists, Colorectal surgeons and Urologists are members of their specialist societies and submit data to their specialist societies' audit databases.
• The MDT composition meets the standards with the exception of a neurologist in the extended MDT.
• Specialist gynaecology, specialist urology and colorectal surgery are co-located. All gynaecologists are subspecialist Urogynaecologists
• There is involvement of Consultant Radiologists with a Special Interest in Female Urology/Urogynaecology.
• Whilst adult critical care services and pain management are co-located, there is not co-located psychological or psychosexual support services for these patients.

Trust C:

The trust simply stated 'Yes'.

Trust D:

The trust, believes that it does meet the standards, pending the standards being confirmed

by the current review and agreement on commissioning standards.

Trust E:

The trust believes that it meets the standards for the following reasons:

All Mesh complication cases are discussed in the Pelvic Floor MDT and all of the appropriate specialists in attendance. All of these personnel are suitably qualified and members of their respective sub specialist groups. The trust collectively has the necessary experience of complex laparoscopic and open pelvic surgery required.

The trust is willing to attend annual clinical summits, as suggested.

The trust is able to offer the full range of investigations listed (with the exception of ambulatory urodynamics which when required can be commissioned from other hospitals).

The trust is able to perform the full range of surgical procedures listed and will frequently operate together to provide the appropriate combined expertise.

The trust suggests that audit data indicates both that there is sufficient demand for this complex work to justify the centre's existence and good results indicating there is no clinical reason that the complex mesh service should not continue to be offered.

Trust F:

The trust simply stated 'Yes'.

Trust G:

The trust simply stated 'Yes'.

Trust H:

The trust notes that the unit would meet the criteria for a specialist centre, but not a mesh removal centre.

Trust I:

The trust expressed that it felt that its unit meets the standards set by the Specialist Commission consultation.

Trust J:

The trust believes that it does meet the standards set for specialist commissioning, citing BSUG accreditation of the Urogynaecology Unit and multidisciplinary work with allied specialities, as required.

Trust K:

The trust is a recognised mesh centre with the British Society of Urogynaecologists (BSUG). All mesh centres put themselves forward for recognition. However, to be registered as a mesh centre, a highly trained multidisciplinary team of Urogynaecologists/Urologists/Colorectal surgeons/Radiologists and Pain management specialists are required, conditions that the trust believes that it meets.

The trust submits to the National clinical database on BSUG, as well as completing MHRA forms for mesh complications, either from within the unit or tertiary referrals. All cases are discussed at Multidisciplinary Team meetings.

Trust L:

The trust simply stated ‘Yes’.

Trust M:

The trust believes that it has the specialist expertise, integrated multi-disciplinary group model of care, high work volume providing local, regional and tertiary referral work, research and academic activity in the field of pelvic floor dysfunction.

Trust N:

The trust reports that its unit meets most of the requirements necessary for a specialised service, providing complex treatments as per the recommendations of the consultation document.

The trust notes that its Pelvic Floor Team has the necessary diagnostic and surgical expertise for appropriate management of recurrent incontinence requiring further surgical intervention. A wide range of stress incontinence procedures are performed in the unit also.

The trust cites a culture of joint working between consultants within the unit. Patients requiring input from multiple specialities such as Urogynaecology, Urology and Colorectal surgery (e.g. combined vaginal and rectal prolapse) are well planned and managed. A thorough face to face discussion is facilitated by the robust Pelvic Floor MDT.

Trust O:

The trust states that its unit meets the standards set by Specialist Commissioning for a Mesh Removal Unit.

Trust P:

The trust states that its unit does comply with the majority of the standards set. Problems involving capacity, waiting times and administrative support for data collection are cited, however. It is noted that funding from trusts/NHSE is required to allow specialists the support to comply with the standards. Access to pain specialists (often required with mesh complications) also involves a rather lengthy wait, according to the trust.

Trust Q:

The trust simply stated ‘Yes’.

xi) Please specify the criteria used to certify as a specialist centre?

Summaries of the individual responses from the mesh centres are laid out below. The majority of trusts simply noted which of the criteria they satisfied.

Trust A:

The unit is accredited by BSUG. Tertiary level urogynaecology is offered and there is close working with urologist (with special interest female urology and neuromodulation) and colorectal surgeons with an interest in functional care. There is urogynaecology subspecialty training programme and the urologist offers specialist training. All cases (not just mesh procedures) are recorded on the database.

Specialist investigations are provided, alongside a broad range of prolapse and incontinence procedures. Joint clinics are offered combining urology, colorectal and Care of Elderly teams. Pelvic floor physiotherapy is offered.

The trust notes a high volume of referrals and patient throughput. A high level of research activity is also noted.

Trust B:

The trust notes that it registered as a specialist centre in September 2016 and followed the criteria specified by BAUS and BSUG.

Trust C:

The trust believes that it fulfils the criteria to be an independent mesh centre (Those stipulated in Pelvic Floor Society and BAUS guidelines – currently being considered as a mesh centre on the BAUS website).

The trust cites an experienced team of urogynaecology, colorectal and urological surgeons as well as regular Joint MDT meetings and regular joint clinics and when required joint operating. The trust states that it has the necessary skills required for mesh removal and have both vaginal and abdominal reconstructive expertise. Access to psychological support and pain team input is mentioned also, alongside plastic surgeon and pain clinic involvement.

Trust D:

The trust gave a lengthy response, which detailed the appropriate professionals that ought to be involved in an MDT, the investigative modalities that should be offered by a specialist centre, as well as appropriate treatment strategies (all involving MDT working). A range of surgical procedures were laid out, including those that might require colorectal/plastic surgeon involvement. Recording of procedures on the BAUS or BSUG databases - as well as reporting complications to the MHRA - was also mentioned. Competency of clinicians (for example, surgeons should be performing more than

10 mesh cases a year, according to the trust) and accreditation of the unit by BAUS/BSUG was stated. Appraisal of the trust/clinicians was an important feature of the response.

Trust E:

The trust cites its response to the previous question as the criteria that have been applied.

Trust F:

Response not given.

Trust G:

The trust noted its constituent professions, MDT working, including urology and colorectal surgery. It is also noted that the trust is already dealing with mesh problems with the mentioned specialties, including pain team and radiology. Reference is made to the use of the BSUG database.

Trust H:

The trust notes that current mesh centres are self-selecting against criteria produced by BSUG and BAUS. Specialist Commissioning will commission future mesh centres.

Trust I:

The unit details the essential requirements as the following:

- A designated urologist, gynaecologist, colorectal surgeon and pain relief specialist
- Patient discussions to be carried out in the setting of a multi-disciplinary team (MDT) meeting
- The application by the centre to be agreed & signed-off by the Trust's Medical Director.

The unit feels that it meets all the specified requirements in the NHS England consultation document, citing the activities below:

- Joint operating by subspecialists.
- Follow up through specialist clinics with PROMS, surgical and other outcomes recorded.
- Data submitted to BAUS and BSUG surgical databases and cases flagged up through the MHRA reporting system.
- Local data is collected for audit and publication.
- Leads for the service engage in the Specialist Commissioning consultation process, attend local network meetings and national meetings to share experiences.
- Working with Surgical Training Centres to develop appropriate surgical training courses (planned BSUG/BAUS affiliation/endorsement).

Trust J:

The trust believes that there are no set criteria as yet to certify specialist mesh centres, nor is there a formal independent certification process. All "specialist centres" are self-declared, based on clinical activity and collaboration with allied specialities. The RCOG and BSUG are almost certainly working on a formal independent certification process. The criteria used to certify the specialist centre can be obtained from the RCOG and BSUG.

Trust K:

The trust uses the BSUG accreditation criteria as a recognised national centre.

Trust L:

The trust cites the activities below:

All data are entered onto to either BSUG or BAUS database.

Reporting of all adverse incidents involving mesh to MHRA, including retrospectively, regardless of whether the surgeon now operating carried out the original procedure.

Discussion of every patient operated on for mesh complications at an MDT prior to surgery. As a minimum a gynaecologist and urologist will be at the MDT and this is documented in the notes.

The following conditions are set out, additionally:

- All surgeons to evidence a minimum caseload of 20 per year to keep up specialty expertise
- All patients are assessed by a co-located, multi-disciplinary team able to offer all treatment modalities as described in the specification.
- All patients to have access to the expertise of a urogynaecologist and a colorectal surgeon with a special interest in anorectal dysfunction.
- Complex Gynaecology Recurrent Prolapse and Urinary Incontinence Surgeons perform minimum number of cases (20) per year to maintain skills.
- Units require defined links to other definition sets and should be co-located with the relevant services. Multi-professional and multi-disciplinary input is required because the patient often has co-morbidities which render the care of the gynaecological disorder especially complex. This is best provided by a sub-specialist centre co-located with other specialised services.
- An auditable register of all implants and their complications is kept locally with a view to developing a national data base.
- All modalities of repair are available so that the woman has the opportunity to have less invasive treatment options

Trust M:

The trust lays out the following criteria, which it fulfils in order to be considered a specialist centre:

- Relevant accredited specialists and team members.

- Specialist consultant led dedicated clinics.
- Locally provided pain and psychology services as part of the assessment pathways and Trust services.
- Compliance with NICE, BAUS and BSUG subspecialty guidance in the relevant areas of incontinence and pelvic floor dysfunction.
- Regular MDT meetings and discussion of cases.
- Co-located theatre lists of urology, urogynaecology and colorectal surgery to facilitate a multi-disciplinary team for relevant complex cases.
- Relevant skills in open, endoscopic, laparoscopic, vaginal and urethral surgery. Access to relevant equipment.
- Regular tertiary referral of cases to our unit from surrounding Trusts.
- Relevant diagnostic facilities available including Ultrasound/ MRI / Videourodynamics.
- Dedicated specialist nurse led clinics.
- Research and publication programme in the field of pelvic floor dysfunction.

Trust N:

The trust notes a strong MDT setup, the scope of which includes the following:

- To discuss all cases with urinary incontinence prior to invasive treatment.
- To discuss all cases where Laparoscopic/ Robotic surgery is being considered for Pelvic Floor dysfunction.
- To discuss all cases where a procedure requiring insertion of a mesh is being considered for Prolapse /Pelvic Floor dysfunction.
- To discuss all cases where joint working with Gynaecology, Urology and Colorectal surgery is considered.
- To discuss any complex cases that members may need advice on
- To audit outcomes and practice against NICE guidance
- To discuss all mesh complications are discussed and ensure reporting to MHRA
- To consider patients for available research trials

There is also mention of offering a sufficient range of investigative modalities and treatment/surgical options.

Trust O:

According to the trust, the criteria used to certify as a specialist centre are:
Regular MDT Working of Urologists with an interest in FNUU urology and Urogynaecologists.

Associated MDT expert clinicians co-located (Uro-Radiology/Functional Colorectal/Genito-Urinary Pain/Medical Scientists/Pelvic Floor Physiotherapy and Continence CNSs).

The trust also offers all investigative modalities on site.

Trust P:

The trust notes that establishment as a specialist centre came after ensuring as robust a governance process as possible. This included reaccrediting with BSUG, gaining external existing expert approval of total laparoscopic TVT removal and expansion of its MDT.

Trust Q:

The trust notes the following criteria:

Available expertise with regularly presented outcomes; colorectal, urogynaecology , pain specialist and urology. For primary cases as well as for recurrent cases of urinary incontinence and prolapse, vaginal mesh complication, mesh erosion, pain and voiding dysfunction.

Pelvic floor MDT, MHRA reporting, registration as a centre for vaginal mesh salvage surgery/management and local auditing are also mentioned.

Sent by email only

3 May 2019

Baroness Julia Cumberlege
Chair
Independent Medicines and Medical Devices Safety Review

Dear Baroness Cumberlege,

Request for information on the implementation of the high vigilance restriction period regarding vaginal mesh in the independent sector

I hope that this letter finds you well.

I'm writing in follow up to our oral evidence session with the Review on 26 March 2019 where I undertook to provide you with the numbers of vaginal mesh procedures undertaken by Independent Healthcare Providers Network (IHPN) members since the implementation of the high vigilance restriction period in July 2018[1]. We have now heard back from all our acute independent hospital members and I can confirm that the total number of these procedures carried out in IHPN member hospitals since July 2018 is seven.

I hope this figure provides you with the information you need, but please let us know if you require anything else. If there is anything further IHPN can do to support the overall work of the Inquiry, please do let me know.

Yours sincerely,

David Hare
Chief Executive

[1] IHPN represents over 98% of all independent acute hospitals in England.