NOT FOR PUBLICATION

COMMISSION ON HUMAN MEDICINES

HORMONAL PREGNANCY TESTS WORKING GROUP

Minutes of the meeting held on Wednesday 14th October 2015 at 10:00 in R-T-501-3, 5th floor, 151 Buckingham Palace Road, London SW1W 9SZ

Members/Experts/Observers Present

Members
Dr A Gebbie (Chair)
Professor P Doyle
Mrs J Epstein
Professor J Harper
Professor Dr A Heep
Professor S Hillier
Ms S Payne
Mrs F Pradhan
Professor S Quenby
Dr R Quinton
Dr C Smith
Dr D Wellesley

Invited Experts
Mr N Dobrik
Professor H Dolk
Professor S Evans
Dr I Petersen
Professor S Price
Professor Dr med C Schaefer
Professor F Williams
Dr L Yates

Observers
Mrs M Lyon
PD Dr E Röhrdanz

Apologies
Dr A Connolly
Mr I Currie
Professor A Macfarlane
Professor K Marshall

Secretariat
Ms F Norris (Secretary)

Professional Staff of MHRA Present

Principal assessors	Item
Dr K Ord	3.1, 3.4 & 3.5

Supporting Specific Items

Dr J Woolley	3.2
Dr M Harrison-Woolrych	3.3

Observers
Dr J Raine
Mrs S Morgan
Mrs P Datta-Nemdharry
Dr J Clements
Dr J Nooney

4/12/15

1. Apologies and Announcements

1.1 The Chair reminded those present that the papers and proceedings are confidential and should not be disclosed and that all mobile phones must be switched off.

1.2 The Chair reminded those present to declare any personal interests (e.g. shares, lecture fees, consultancy, travel/accommodation costs or other direct remuneration) in the following associated companies (all successors of the companies who originally marketed HPTs):

- Alinter Group
- Bayer plc
- GlaxoSmithKline UK
- Marshall's Pharmaceuticals Ltd
- Merck, Sharpe and Dohme Ltd
- Pfizer
- Piramal Healthcare Ltd
- Sanofi

The Chair also reminded those present to declare the nature of any involvement they may have had with HPTs (e.g. reviews of these products, public commentary on their safety).

1.2.1 The Group commented that involvement in any related litigation would be another important conflict of interest.

1.3 Apologies were received from:

- **Dr Anne Connolly**
- **Mr Ian Currie**
- **Professor Alison Macfarlane**
- **Professor Kay Marshall**

1.4 The Chair informed those present that the following experts will no longer be members of the group:

- **Dr Tony Salmon**
- **Professor Joan Morris**

2. Matters arising

2.1 Mrs Lyon raised concerns about the restrictions of observer participation. The Chair reassured Mrs Lyon that she would make a point to ask her to contribute.

3. Papers

3.1 Introduction and background to the review of Hormonal Pregnancy Tests (paper 1)

3.1.1 The Group noted MHRA paper 1.

3.1.2 The Group discussed a number of key issues relating to paper 1 and established that by 1978 HPTs were no longer available in the UK for any indication, including secondary amenorrhoea. The Group commented that women exposed to HPTs could possibly also have been co-prescribed thalidomide or other teratogens and that it would be important to take this into account when looking at the epidemiological evidence. However, although limited usage data for HPTs are available, it is less likely that good records were kept for co-prescribed products. The Group commented that the lack of good data collection practices at that time is a factor that will need to be taken into consideration throughout this review; GPs may have given HPTs out as free samples. Similarly, the Yellow Card System was considered to have limitations for detecting congenital anomalies.

3.2 Structure and remit of the Expert Working Group on Hormonal Pregnancy Tests and agreement of Terms of Reference (paper 2)

3.2.1 The Group noted Tabled Papers I and II.

3.2.2 The Group noted MHRA paper 2, which included the proposed terms of reference for the EWG as follows:

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

3.2.3 The Group noted the conflicts of interest policy for the EWG and the proposal to present the Group's findings to the Commission on Human Medicines, followed by publication.

3.2.4 The Group commented that the purpose of the review, as specified in paper 2, should be re-phrased to clarify that the EWG will consider the strength of evidence for an association between use of HPTs and adverse effects on pregnancy rather than being able to establish causality.

3.2.5 It was clarified that the remit of the Group included reviewing all forms of scientific evidence (including non-clinical data) but that it would also be free to comment on cultural/systemic issues as appropriate. It was agreed that the lay members' role included scrutiny of the work of the EWG.

3.2.6 The Group agreed to revisit the terms of reference at the end of the meeting, to determine whether they were appropriate.

3.3 A brief history of pregnancy testing, socio-medical landscape and medicines regulation in the UK (paper 3)

3.3.1 The Group noted MHRA paper 3, which included the history of pregnancy testing and the use of HPTs, the social and medical environment for women during the 1950s to 1970s and the history of medicines regulation and the relevant legislation in the UK.

3.3.2 The components of HPTs were, and in many cases still are, components of combined hormonal contraceptives (CHCs), albeit at different doses. The Group questioned whether there was any good evidence on the risk of miscarriage with HPTs. It was noted that studies of pregnancy outcomes in women exposed to CHCs were reassuring with respect to spontaneous abortion and miscarriage but the doses were lower than HPTs. The Group further commented that even very large studies with CHCs were underpowered to detect an association with congenital anomalies (unless the effect size was marked and similar to that seen with thalidomide).

3.3.3 When reviewing any possible association the Group thought it would be important to consider whether there was a particular type or group of women who received HPTs but acknowledged that the documented evidence on this may be limited. The experience of members of "the Association" was that the majority of women were first time mothers and were given the HPT tablets without any discussion.

3.4 Overview of HPT products available and chronology of events in the UK and worldwide (paper 4)

3.4.1 The Group noted MHRA paper 4, which documented the HPTs that had been available, and their estimated exposure, in the UK. The Group noted the chronology of events relating to HPTs in the UK and worldwide, including the first published report in 1958 by Dr Edwards, a study by Gal et al (published in 1967) which raised concern that HPTs may be associated with spina bifida, and a number of subsequent studies of the effect on HPTs on a variety of congenital anomalies. The Group noted the actions taken by regulators and the companies which marketed HPTs to investigate whether HPTs may be associated with birth defects, the regulatory action taken by the Committee on Safety of Medicines, the withdrawal of the products for commercial reasons in the 70s and historical and current media and parliamentary interest in this issue. The Group noted that the chronology of events would be updated if further information is obtained (including from documents in German provided

by the Association).

3.4.2 Because of the different pharmacological and pharmacokinetic properties of the sex steroids, the Group agreed that it would be important to clearly define what hormones women had received in the studies that have been carried out and to agree which hormones should fall within the scope of the review. The Group commented that there was little evidence that sex steroids, including norethisterone (NET, the progestogenic component of Primodos), are teratogenic and considered that it would be essential to understand how the high progestogenic doses in HPTs compare to: naturally occurring doses of progesterone; the high doses of progesterone found throughout pregnancy; and the doses (~600mg progesterone/day) used to prevent miscarriage in early pregnancy. It was agreed that there is clear evidence of a virilising effect with use of high dose NET.

3.4.3 The Group questioned whether data on accidental exposure to hormonal contraceptives, or to other high dose progestogens in pregnancy (including Cumorit and steroid implants) could be useful in investigating a possible association between sex hormones and congenital anomalies. It was noted that previous studies on congenital anomalies with CHCs (including up to 8000 pregnancies) have been too small to determine whether there is any association and other risk factors and behaviours in contraceptive users would also need to be considered.

3.4.4 The Group recognised that historical clinical data was likely to be of limited value as there was no electronic collection of such data. It was also noted that there did not appear to have been compliance by healthcare professionals with the advice of the Committee on Safety of Medicines in relation to HPTs.

3.4.5 The Group felt it would be important to consider whether barriers to data collection at the time HPTs were available remain barriers in the context of the current regulatory system and considered that suggestions for improvement could form part of the recommendations of the EWG.

3.5 Programme of work, summary of information, proposed topics for future meetings (paper 5)

3.5.1 The Group noted MHRA paper 5, which summarised the evidence which had been collated for the EWG to consider and proposed a programme of work for the Group.

3.5.2 The Group discussed a number of key issues relating to this paper, and, in light of the limitations of historical data and studies in animals, suggested the following aspects could also be explored as part of the review:

- consideration of the pattern of malformations in affected individuals and

the possible contribution of genetics to the reported adverse effects in pregnancy, including the possibility of offering individuals genetic testing and examining epigenetic data, if available;

- consideration of all evidence on potential mechanisms of action (including current as well as historical data), and direct and indirect effects on the pregnancy – where data is lacking expert opinion would be valuable;
- consideration of the influence of various factors on the risk of adverse effects in pregnancy including time of exposure, dose, maternal age and medical histories and consideration of the clinically relevant effect size;
- further understanding of the pharmacology of HPTs and their components, including isoforms, potency, purity, and medicinal chemistry;
- consideration of changes in the regulatory framework for toxicology from the 60s and 70s in terms of types of studies (segment II and III in particular), species, numbers, strains etc
- consideration of performing a systematic review of the evidence;
- establishing pregnancy/outcome/congenital anomaly registries;
- the possibility of collecting information and recollections from those involved with HPTs at the time they were available and on how these products were used;
- recollections from individuals who consider themselves to have been affected by HPTs;
- possible use of subgroups of the EWG to explore some of the issues

3.5.3 The Group considered that pharmacology, pharmacokinetics/medicinal chemistry, (repro)toxicology and teratogenicity data would be important considerations. In this respect it would be helpful to have additional expertise in pharmacology and pharmacokinetics, and additional expertise on communications.

3.5.4 The Group was informed that an independent scientist had been performing studies of the components of Primodos and their findings could be presented to the Group at a future meeting. The Group commented that it would need to formally assess the data as evidence in the review.

3.5.5 The Group considered it would be important to identify the lessons that may be learned from this issue to ensure that current drug regulatory systems are adequate for the detection of drug safety issues for medicines used in pregnancy, that risk minimisation, communication and prevention are robust, and compliance with regulatory recommendations is monitored.

4. General Discussion

4.1 The Group reconsidered the terms of reference for the review in light of the

discussion and suggested that these could be amended to more widely capture adverse effects on pregnancy (rather than limiting only to congenital anomalies) as well as to capture what lessons may be learned to improve current regulatory systems and processes.

4.2 The terms of reference for the Group were therefore amended and agreed as follows:

1. To consider all available evidence on the possible association between exposure in pregnancy to HPTs and adverse outcomes in pregnancy (in particular congenital anomalies, miscarriage and stillbirth) including consideration of any potential mechanism of action;

2. To consider whether the Group's findings have any implications for currently licensed medicines in the UK or elsewhere;

3. To draw any lessons for how drug safety issues in pregnancy are identified, assessed and communicated in the present regulatory system and how the effectiveness of risk management is monitored;

4. To make recommendations.

5. Any other Business

5.1 None.

6. Date and Time of Next Meeting

6.1 Friday 4th December 2015 at 10am.

Members are reminded that the content of papers and proceedings of the meeting are to be treated as 'Restricted - Commercial'. Members are also reminded that, in accordance with the Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members must also declare any other matter which could reasonably be perceived as affecting their impartiality. Detailed guidance is set out in the Code of Practice.

NOT FOR PUBLICATION

COMMISSION ON HUMAN MEDICINES

HORMONAL PREGNANCY TESTS WORKING GROUP

Minutes of the meeting held on Friday 4th December 2015 at 10:00 in R-T-501-3, 5th floor, 151 Buckingham Palace Road, London SW1W 9SZ

Members/Experts/Observers Present

Members

Dr A Gebbie (Chair)
Professor P Doyle
Mrs J Epstein
*1 Professor J Harper
Professor S Hillier
Professor A Macfarlane
Ms S Payne
Mrs F Pradhan
Professor S Quenby
Dr R Quinton
Dr C Smith

Invited Experts

Dr A Connolly
Mr N Dobrik
Professor H Dolk
Professor K Marshall
Dr I Petersen
Professor S Price
Professor F Williams
Dr L Yates

Observers

Mrs M Lyon

Visiting Experts

*2 Professor D Healy

Apologies

Mr I Currie
Professor S Evans
Professor Dr A Heep
PD Dr E Röhrdanz
Professor Dr med C Schaefer
Dr D Wellesley

Secretariat

Ms F Norris (Secretary)

Professional Staff of MHRA Present

Principal assessors	Item
Dr J Beynon	3.2

Supporting Specific Items

Dr K Ord	3.2
Dr J Woolley	3.2

Observers

Mrs S Morgan
Dr J Nooney

*1 *left at 13:30 during item 5*

*2 *presented item 3.1 and left after discussion of this item*

11/5/2016

1. Apologies and Announcements

1.1 The Chair reminded those present that the papers and proceedings are confidential and should not be disclosed and that all mobile phones must be switched off.

1.2 The Chair reminded those present to declare any personal interests (e.g. shares, lecture fees, consultancy, travel/accommodation costs or other direct remuneration) in the following associated companies (all successors of the companies who originally marketed HPTs):

- Alinter Group
- Bayer plc
- GlaxoSmithKline UK
- Marshall's Pharmaceuticals Ltd
- Merck, Sharpe and Dohme Ltd
- Pfizer
- Piramal Healthcare Ltd
- Sanofi

The Chair also reminded those present to declare the nature of any involvement they may have had with HPTs (e.g. reviews of these products, public commentary on their safety).

Mr Ian Currie and Professor Alison Macfarlane confirmed that they had no interests in advance of the meeting of 14th October 2015. A list of the remaining participants' interests was circulated in advance of the October meeting.

1.3 The Chair welcomed:

Professor David Healy MD FRCPsych
Professor of Psychiatry, Bangor University

who attended as a visiting expert for item 3.1.

2. Matters arising

2.1 The Group agreed the minutes of the meeting held on 14th October 2015.

2.2 The Group agreed the updated terms of reference for the Group, as follows:

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

3. Presentations

3.1 Spontaneous reporting systems and their strengths and limitations, particularly with respect to detecting/identifying birth defects and adverse effects on the pregnancy (Professor David Healy)

3.1.1 The Group was informed that views on the strengths of spontaneously-reported adverse drug reaction (ADR) data range from being regarded as anecdotal accounts to being the best available evidence in certain situations (particularly when positive de-challenge and re-challenge data are available).

3.1.2 The Group noted the limitations of such data in accurately determining incidence rates, difficulty in identifying events with long latency and de-challenge and re-challenge not being possible for some ADRs, including birth defects. The Group was informed of Professor Healy's view that some Marketing Authorisation Holders may miss potential signals arising from spontaneously-reported ADR data because related events are analysed separately rather than as a group.

3.1.3 The Group was informed of Professor Healy's view that data from randomised controlled trials can be helpful but may be of limited value if not adequately designed to identify a particular risk or if it is not known which risks may occur.

3.1.4 The Group was informed that pregnancy registries are of most use in identifying congenital anomalies. The Group agreed that benefits of such registries include their ability to capture information on all medicines taken and to follow-up the child for several years. However, they can also have limitations in terms of the quality of data collected and the voluntary nature of participation in such registries.

3.1.5 The Group noted that all medicines are subject to post-marketing surveillance and all vaccines subject to active surveillance. The Group further noted that all new medicines require a risk management plan, in which the need for post-marketing studies (which can include pregnancy registries) to further characterise any potential risks are discussed.

3.1.6 Professor Healy then informed the Group about his observations in relation to selective serotonin reuptake inhibitors and developmental disorders.

3.2 Spontaneously-reported adverse drug reaction cases and individual case reports involving adverse effects of HPTs on pregnancy

3.2.1 The Group noted Tabled Papers I and II.

3.2.2 The Group noted MHRA paper I, which included spontaneously-reported ADR data collated from the following sources:

1. Information from MHRA safety database (Yellow Card scheme)
2. Information submitted through the public call for evidence, including Information on the malformations and adverse effects on pregnancy reported in association with HPTs in the UK and Germany, and patient testimonials
3. Information provided by pharmaceutical companies (specifically a summary of anonymised litigation cases)
4. Information provided by the UK Teratology Information Service
5. Information from other regulatory authorities worldwide and the World Health Organisation.

3.2.3 The Group noted the estimated total number of cases reported from all sources in association with use of each HPT (768 cases reported with ethinylestradiol/norethisterone; 27 cases reported with ethinylestradiol/ethisterone; and 36 cases reported with an unknown HPT) and acknowledged that the number of unique cases is unknown because of the overlapping datasets.

3.2.4 The Group noted that, with exception of data provided by The Association, in the majority of cases, information on maternal medical, drug and social history and family history was not available. The Group noted that the number of cases reported through the Yellow Card scheme was small and may reflect a lack of awareness of this method of reporting and the lack of a mechanism for patient reporting at the time HPTs were available. The Group suggested that it may also represent reluctance to report an adverse outcome if the medicine was used off-label (e.g. as an abortifacient).

3.2.5 The Group noted the most commonly-occurring anomalies (either "as–reported" terms or by MHRA selection of an appropriate MedDRA preferred term for patient-reported outcomes) were musculoskeletal (including limb malformation), heart, craniofacial, gastrointestinal, nervous system, spinal and urinary system defects. The Group considered that the cases suggested there may be an excess of limb and musculoskeletal defects relative to other anomalies and that it would be important to further investigate this. One way could be to compare the proportion of such defects reported with Primodos with the proportions reported in the overall population.

3.2.6 The Group commented that it would be helpful to see what events were most frequently reported together to see if any syndromes could be identified.

3.2.7 The Group did not consider it possible to draw conclusions on the information presented due to the limitations of the available data, and recommended that a number of options for further work could be explored before any conclusions could be drawn including:

- Obtain further details of litigation cases to better define and classify the reported anomalies;
- Trying to identify duplicate cases;
- Performing a hierarchical classification of the reported anomalies with assistance from a medical geneticist (where multiple anomalies with limb components should be captured within any limb group);
- Examining whether there was any pattern of combined defects
- Examining whether any relationship exists between the reported anomalies and dose, timing of exposure), and gender.
- Statistical evaluation of reports of congenital anomalies received.

It was agreed that an update would be provided to the Group.

4. Personal experiences of people affected by HPTs

4.1 The Group initially heard directly from 12 members of the Association for Children Damaged by HPTs, about their experiences. These included the following people:

- [redacted] who described her experiences with her son
- [redacted]

4.2 Due to unforeseen travel delays, the following family (member of the Association for Children Damaged by HPTs) arrived after the meeting had closed:

- [redacted] (Carer)

The Secretariat was able to reconvene the meeting to hear about the family's experience from 14:31 – 14:45, with the following participants of the Group present:

- Mr Nick Dobrik
- Professor Helen Dolk
- Professor Pat Doyle
- Mrs Joyce Epstein
- Dr Ailsa Gebbie
- Professor Stephen Hillier
- Mrs Marie Lyon
- Professor Alison Macfarlane
- Professor Kay Marshall
- Dr Irene Petersen
- Professor Shirley Price

4.3 The Group heard each person's description of their individual experience, including the circumstances in which the HPT had been given or prescribed to them, the time at which they were exposed during the pregnancy, information about the use of HPTs during any previous or subsequent pregnancies and the outcome. Details of each of the wide range of anomalies which had occurred were described together with the impact that these had on their lives or those of their children (or both). The Group requested further information where they thought this was relevant and all individuals were asked if there was anything else they would like to add.

4.4 The Group commented that these were powerful testimonials that were important to consider alongside the other evidence.

5. General Discussion

5.1 The Group noted comments from the Chair of the Association for Children Damaged by HPTs regarding the evidence presented, and the review, including

- Clarification that the events reported by patients were historically-reported events rather than newly-identified events, and that the Association had approximately 700 members at its peak;
- Some of the members of the Association have had genetic testing which confirmed there was no evidence of genetic anomalies present;
- The reported anomalies are unusual and wide-ranging, similar to those reported for thalidomide;
- Studies from Bayer had been provided for the review which showed anomalies but these have not been presented to the Group;
- The Association's request that Professor Healy be a member of the Expert Working Group has not been honoured.

5.2 The Group asked the Chair of the Association to thank the members for sharing their experiences, and agreed that a complex pattern of anomalies had been described.

5.3 The Group suggested it would be important to obtain data from a larger cohort rather than reviewing individual anecdotal accounts. The Group suggested it may be possible to identify further potential cases by reviewing historical GP records to identify all women prescribed or given HPTs and following up the outcomes of these pregnancies. The Group also suggested that genetic testing would help to identify whether reported anomalies may have a genetic component and recognised this could be a recommendation of the Group. The Chair of the Association agreed to provide the Group with further details of the results of genetic testing on members of the Association.

6. Matters arising

6.1 The Chair clarified that although subgroup working had been considered for some aspects of the Group's work, it would be preferable for the whole Group to be involved, with individual experts approached to advise the rest of the Group on their specialist areas.

6.2 It was confirmed that no progress had been made with contacting the experts who may have had involvements with HPTs at the time these products were available.

6.3 The Group made recommendations for a number of additional experts to invite to join the Group, including experts from the Far Institute, Bev Botting, Nirupa Dattani, Geoff Tucker and Leon Aarons.

6.4 It was suggested that the Commission on Human Medicines could provide information on their approach to collecting data on the impact of changes to prescribing information for sodium valproate.

6.5 It was suggested that Bayer be approached to obtain further details of the litigation cases, if this does not impact on the legal privilege.

7. Any other Business

7.1 None. The meeting closed at 14:13.

8. Date and Time of Next Meeting

8.1 Monday 25th April 2016 at 10am.

Members are reminded that the content of papers and proceedings of the meeting are to be treated as 'Restricted - Commercial'. Members are also reminded that they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members must also declare any other matter which could reasonably be perceived as affecting their impartiality.

NOT FOR PUBLICATION

COMMISSION ON HUMAN MEDICINES

HORMONAL PREGNANCY TESTS WORKING GROUP

Minutes of the meeting held on Monday 25th April 2016 at 10:00 in R-T-501-3, 5th floor, 151 Buckingham Palace Road, London SW1W 9SZ

Participants Present

Members

Dr A Gebbie (Chair)
Mrs J Epstein
Professor Dr A Heep
[1] Professor S Hillier
Professor A Macfarlane
Ms S Payne
[2] Mrs F Pradhan
Professor S Price
[3] Dr C Smith
Professor M Threadgill
[5] Dr D Wellesley

Invited Experts

[1] Professor L Aarons
Mr N Dobrik
Professor H Dolk
Professor S Evans
Professor K Marshall
Dr I Petersen
Professor F Williams
Dr L Yates

Observers

Mrs M Lyon
[4] PD Dr E Röhrdanz

Professional Staff of MHRA Present

Supporting Specific Items	Item
Dr J Beynon	3.3
Dr J Nooney	5
Dr J Clements	5
Ms S Cole	5

Observers

Mr M Dykes (COMMS)
Mrs S Morgan (VRMM)
Dr K Ord (VRMM)
Dr J Raine (VRMM)
Dr J Woolley (VRMM)

18/10/16

Apologies

Dr A Connolly
Mr I Currie
Professor P Doyle
Professor J Harper
Professor S Quenby
Dr R Quinton

1 *Left during the afternoon break (15:05-15:20), which took place during item 5*
2 *Left during the lunch break (12:25-13:51), which took place during item 5*
3 *Left at 16:13, during item 5*
4 *Left at 14:40, during item 5*
5 *Presented item 4.1*

Secretariat
Ms F Norris (Secretary)

MHRA Legal
Ms K Foster

1. Introduction and Announcements

1.1 The Chair reminded those present that the papers and proceedings are confidential and should not be disclosed and that all mobile phones must be switched off.

1.2 The Chair welcomed:

Professor Michael D Threadgill PGCE MA PhD DSc FRSC CChem
Professor in Medicinal Chemistry, Department of Pharmacy and Pharmacology, University of Bath

who joined as a new Member of the HPTWG.

1.3 The Chair welcomed:

Professor Leon Aarons BSc MSc PhD ICI
Professor of Pharmacometrics, Manchester Pharmacy School, The University of Manchester

who joined as a new Invited Expert of the HPTWG

1.4 Apologies were received from:

- **Dr Anne Connolly**
- **Mr Ian Currie**
- **Professor Pat Doyle**
- **Professor Joyce Harper**
- **Professor Siobhan Quenby**
- **Dr Richard Quinton**

1.5 The Chair reminded those present to declare any personal interests (e.g. shares, lecture fees, consultancy, travel/accommodation costs or other direct remuneration) in the following associated companies:

Successors of the companies who originally marketed HPTs:

- Alinter Group
- Bayer plc
- GlaxoSmithKline UK
- Marshall's Pharmaceuticals Ltd
- Merck, Sharpe and Dohme Ltd
- Pfizer
- Piramal Healthcare Ltd
- Sanofi

The companies who originally marketed HPTs:

- Roussel Laboratories

- Parke Davis
- Wallace Manufacturing Chemists Ltd.
- Schering
- Organon Laboratories
- Nicholas Laboratories Ltd.
- Duncan Flockhart and Company Ltd.

The Chair reminded those present to declare the nature of any involvement they may have had with HPTs (e.g. reviews of these products, public commentary on their safety).

The Chair advised that the new participants to the HPTWG have declared the following:

- **Professor Leon Aarons:** "departmental research funding in Pfizer. This is generic funding for our academic research and pertains mainly to drug metabolism. I have never worked with HPTs".

  The Chair advised that Professor Aarons has therefore been placed into the Invited Expert category.

- **Professor Michael Threadgill:** "I have no current conflicts of interest for any of the companies and other bodies concerned and I have not been involved in in any campaigning or strong opinions in this area. For the sake of completeness, I declare that my research group collaborated with and received a small (approx. £2000) amount of research funding from Sterling Winthrop 1992-1995 on a project to assay theophylline in biosamples for patients being treated for asthma and related disorders (nothing to do with pregnancy testing); part of Sterling Winthrop went on to become part of Sanofi a few years later. This relationship ceased over twenty years ago when the project ended".

  The Chair advised that following legal advice, Professor Threadgill has been placed in the Member category.

The Chair directed participants to **Tabled Paper III** – an updated list of interests declared by the HPTWG.

The Chair advised that the following Members and Invited Experts have declared the following additional interests:

- **Professor Stephen Hillier:** "I delivered lectures at international scientific meetings sponsored by Organon or Schering, as follows:

- Cellular Aspects of Preovulatory Folliculogenesis in Primate Ovaries Symposium to mark the 50th anniversary of Organon France September 1987, Paris, France.
- Follicular Function in Polycystic Ovaries Symposium on 'Chronic Hyperandrogenic Anovulation' October 1989, Oss, The Netherlands.
- Are estrogens of importance to ovarian function? Ernst Schering Research Foundation Workshop 46: New Molecular Mechanisms of Estrogen Action and their Impact on Future Perspectives in Estrogen Therapy March 5-7 2003, Berlin, Germany.

As a PHD student (1972-1975), I participated in the development of assay methods for Norethindrone Acetate and Norgestrel, resulting in the following publications:

- Hillier, S.G., Jha, P., Griffiths, K. & Laumas, K.R. (1977) Long-term contraception by steroid-releasing implants. VI. Serum concentrations of Norethindrone in women bearing a single silastic implant releasing Norethindrone acetate. Contraception 15: 473-488.
- Thomas, M.J., Danutra, V., Read, G.F., Hillier, S.G. & Griffiths, K. (1977) The detection and measurement of D-Norgestrel in human milk using Sephadex LH-20 chromatography and radioimmunoassay. Steroids 30: 349-361".

- **Professor Shirley Price:** "At the University of Surrey as part of my job specification I have organised and taught on a Master's/CPD programme in Applied Toxicology (1996-2014) which was designed to educate and train scientists in the field of Toxicology. This programme attracted delegates and guest lecturers from Pharma Industries, Academia, Agrochemical and Chemical Industries, Cosmetic Industries and Regulatory Authorities. Of the companies listed above GlaxoSmithKline, Pfizer and Sanofi sent students/delegates to attend modules either for CPD or to gain an academic qualification. Members of staff also lectured on the programme from these three companies. The delegates paid a tuition fee to the University of Surrey for attendance to the one week modules".

- **Professor Faith Williams:** "I received non personal research funding of a member of staff in my team at Newcastle between 2004 and 2007".

- **Dr Laura Yates:** "Unconditional funding from GSK and Baxter, the manufacturers of the two swine flu vaccines available in the UK during

the 2009/10 H1N1 pandemic was provided to NUTH (the Newcastle upon Tyne Hospitals NHS Foundation Trust) to support the extension of an existing NIHR HTA funded study - 'H1N1 in Pregnancy Study' - to include the collection by UKTIS of observational prospective outcome data on women vaccinated during pregnancy with the influenza vaccines, Pandemrix (GSK) and Celvapan (Baxter)".

The Chair advised that there were no changes to the status of the Members and Invited Experts in light of the new interests declared.

The Chair advised that responses regarding updated interests have not been received from the following participants:

- **Dr Anne Connolly**
- **Mr Ian Currie**
- **Professor Helen Dolk**
- **Professor Pat Doyle**
- **Professor Stephen Evans**
- **Professor Joyce Harper**
- **Mrs Marie Lyon**
- **Professor Alison Macfarlane**
- **Dr Irene Petersen**
- **Professor Siobhan Quenby**
- **Dr Richard Quinton**
- **Dr Connie Smith**

1.6 The Chair advised that all declared conflicts of interest were being dealt with very carefully and that following receipt of an updated declaration of interests, **Professor Dr Christof Schaefer** will no longer participate in the HPTWG. No concerns were raised at this announcement.

2. Minutes from the meeting of 4th December 2015

2.1 The minutes of the meeting held on 4th December 2015 were adopted as a true and accurate record of the proceedings, with no amendments.

3. Matters Arising

3.1 Concerns raised by Mrs Lyon

3.1.1 The Chair referred to complaints received by the Secretariat from the Chair of the Association for Children Damaged by HPTs (ACDHPTs) (detailed in **Tabled Paper II**) and proposed that this be discussed at the end of the meeting.

Mr Dobrik said that it was vital that the voice of the victims was heard during

the meetings. The Chair of the HPTWG reminded the Group that the Chair of the ACDHPTs had 'Observer' status but agreed to ask for comments at appropriate times.

Some participants of the Group expressed concern that the bulk of the papers had only been circulated on 15th April, giving members only 9 days to read the papers prior to the meeting. Mr Dobrik asked whether the meeting should be postponed as a result but the Group agreed it would be useful to continue. The Secretariat was asked to consider this and ensure that papers were available earlier for future meetings.

The Group commented that information had been circulated just prior to the meeting by the Chair of the ACDHPTs and agreed that any claims made about HPTs needed to be supported by evidence and discussed in the context of the meetings. The Group was advised that all correspondence to members should go through the Secretariat.

Mr Dobrik mentioned that he was awaiting a response from MHRA to a query. MHRA agreed to look into any outstanding correspondence.

3.2 Terms of reference

3.2.1 The MHRA's legal representative reminded the Group of the Terms of Reference and explained the difference between a 'review' and 'statutory inquiry'. This should be borne in mind when considering the operation and function of the Group and emphasised that the work of the Group is a scientific review and not an Inquiry. The Chair of the ACDHPTs asked what practical difference this made. The legal representative confirmed that it did not alter the Terms of Reference for the Group. The VRMM Director explained that the Group's conclusions and recommendations would be presented to the Commission on Human Medicines (CHM) which would advise the Minister as Licensing Authority. The report that is published at the end of the review remains to be discussed but should be transparent.

3.2.2 The Chair asked for Mrs Lyon's input and gave her the opportunity to comment.

3.3 Update on ADR Work

3.3.1 The Group was informed that additional work requested at the last meeting to formally code the reported adverse reaction terms, identify duplicate cases, and group reported anomalies so as to enable possible syndromes to be identified, was ongoing and would be presented at the next meeting.

3.3.2 The Chair asked for Mrs Lyon's input and gave her the opportunity to comment.

4. Presentation

4.1 Current update on congenital anomalies

4.1.1 The Group noted **Tabled Paper I** and heard a presentation from Dr Wellesley, Consultant in Clinical Genetics on the current state of knowledge regarding aetiologies of congenital anomalies. The Group was informed that genetic testing techniques had advanced considerably in the last 5 years and many genetic conditions occurring through chromosomal abnormalities or single gene defects were now known to occur in individuals with no prior family history; these changes arise prior to conception. It was considered possible that current methods of genetic testing could identify the cause of the anomalies suffered by some members of the ACDHPTs. The Chair of the ACDHPTs agreed to check how many of the members had been genetically screened in the last 5 years.

4.1.2 Examples of common anomalies such as neural tube defects (NTD), heart defects and cleft lip and/or palate tended to be multifactorial (genetic plus environmental) but to date few environmental factors (such as folic acid deficiency and NTDs) had been identified and in most cases the cause of an anomaly is unknown.

4.1.3 A number of possible mechanisms of teratogenicity have been proposed in the scientific literature. Of these the Group considered that vascular disruption could be relevant to HPTs if their administration resulted in a bleed in a pregnant woman and that this merited further consideration as a possible mechanism. Evidence to support vascular disruption as a possible mechanism for anomalies comes from Chorionic Villous Sampling (CVS[1,2]) (the timing of which had been changed to >11 weeks of pregnancy following concerns about a link between limb abnormalities with earlier sampling times), and administration of misoprostol, which has been associated with anomalies when taken as an abortifacient in the second month of pregnancy[3,4,5].

4.1.4 The Group commented that in the future it would be helpful to have a register of all drugs taken by pregnant women together with a nationwide register of malformations. The Group was informed that several congenital anomaly registries exist which cover about half of the country and that Public Health England was working to bring together existing registries with the aim of national coverage. The Group agreed that an update on the current position would be useful for a future meeting.

---

[1] Firth et al Lancet 1991;337:762-3
[2] Olney et al, Report from US Centre for Disease Control and Prevention, 1995
[3] NEJM 1998; 338(26): 1881-5
[4] Lancet 1998; 351: 1624-7
[5] AJMG 2000; 95: 302-6

4.1.5 The Chair asked for Mrs Lyon's input and gave her the opportunity to comment.

5. Paper

5.1 Effect of norethisterone acetate (NETA) and ethinylestradiol (EE) on early pregnancy and fetal development

5.1.1 The Group considered the paper on the available evidence from pre-clinical data relevant to a possible association between use of NETA/EE as a HPT and an adverse effect on pregnancy or fetal development (main paper and Annexes III, a review of the pharmacokinetics and pharmacology, and IV, a review of non-clinical evidence. The Group noted that the papers focussed mainly on the active ingredients in Primodos because this was the most widely-used HPT in the UK and both EE and NETA were also found in other HPTs. The Secretariat confirmed that any additional scientific data of relevance to the papers under consideration would be presented to the Group at the next meeting.

5.1.2 The Group expressed concern that some of the questions which had been included in the papers to structure the discussion were phrased in a directional way and asked that these be re-phrased in a neutral manner for the next meeting.

5.1.3 ***Pharmacokinetic/pharmacological considerations***

5.1.3.1 The Group considered the main paper and its Annexes (II and III). These papers described the role of natural estrogens and progesterone during pregnancy and went on to examine the properties and functions of the ingredients in Primodos in the body, including in pregnancy and in the fetus. The aim of the papers was to help determine whether direct pharmacological actions of EE or norethisterone (NET) could have potentially affected early pregnancy or fetal development following maternal exposure to HPTs.

5.1.3.2 Based on the critical period of organogenesis and the time during pregnancy that women were most commonly given HPTs the Group thought this review should only consider studies with HPT exposures between gestation (ie time since last menstrual period, LMP) weeks 4 to 12; exposures outside of this timeframe would not be comparable to the timing of HPT administration for diagnosing pregnancy.

5.1.3.3 Based on the pharmacokinetic data presented, the Group considered that the ranges of plasma levels of EE and NET in non-pregnant women were likely to be reasonably representative of plasma concentrations in pregnant women. The Group commented that any estimates of plasma concentrations should be presented as a range in terms of mass and molarity. It was commented that the metabolism and pharmacological activity of metabolites of NET and EE was not fully understood and the levels of the sulphate conjugates which are particularly high in plasma may contribute to the duration of the effects due to recycling back into the parent steroid.

5.1.3.4 In general the Group considered that it was not possible to extrapolate data from the pharmacokinetic studies conducted in animals to humans because of the large number of variables, inter-subject variability, the uncertainties within the data and the lack of data in general but particularly in human pregnancy and the fetus. Nevertheless, it was considered that the estimated maximum plasma concentrations of free EE and NET provided by a dose of Primodos were likely to be biologically significant in the mother. The levels that were likely to reach the fetus were considered to be lower, but the lack of data on for example, protein binding in the placenta and fetus, precluded a reliable estimate of fetal exposure levels.

5.1.3.5 The Group noted that EE has been described to work solely through estrogen receptors whereas NET can activate progesterone and androgen receptors at similar concentrations and can weakly activate estrogen receptors at high concentrations. The Group also noted that data from animal studies suggests that estrogen and progesterone receptors are expressed towards the end of major organ development in laboratory animals, but it was not clear from the available data at what stage the receptors could be biologically active. The Group considered there was likely to be expression of estrogen and progesterone receptors in the developing fetus but there remains uncertainty as to their precise location and biological activity.

5.1.3.6 The Group noted that knock-out mice which lack estrogen or progesterone receptors are born without anatomical abnormalities and reach adulthood but have functional deficits related to reproduction and reproductive behaviours. The Group considered that it would be worth looking at corresponding human mutations.

5.1.4 ***Non-clinical data***

5.1.4.1 The Group considered the available evidence from pre-clinical data relevant to a possible association between use of NETA/EE as a HPT and an adverse effect on pregnancy or fetal development (main paper and Annex IV). These data described a number of reproductive and developmental toxicity studies evaluating the effect of EE and/or NET on pregnancy outcome in mice, rats, guinea pigs, rabbits and non-human primates. The Group noted that all studies had some limitations because they were conducted before best practice guidelines were in place.

5.1.4.2 The Group heard that embryo-lethality was observed in studies with high dose EE given during organogenesis across a range of species. A similar effect was seen with NET.

5.1.4.3 The Group commented that the timing of dosing animals with NET, with respect to both the period of gestation and duration of exposure, was important to consider when interpreting the results. In particular, the Group questioned whether differences in embryo-lethality could be observed

depending on whether NET was given intermittently or continuously. Also, given that NET has different actions at the receptor depending on dose, the Group questioned whether there is any evidence that lower doses have greater adverse effects.

5.1.4.4 The Group noted that virilising effects were observed in some of the animal studies. The Group considered that virilising effects were to be expected for NET and that such an effect required functional androgen receptor expression by the fetus and administration of NET at the right dose during organogenesis.

5.1.4.5 The Group commented that there were no data to link the observed embryo-lethality to any adverse effects and that overall the available animal data did not suggest a link between NET and non-genital anomalies.

5.1.4.6 Mr Dobrik questioned the completeness of a table listing the malformations identified in studies considered to be most relevant to present to the Group in the meeting. The MHRA confirmed it would check that the papers contained all malformations identified in the animal studies using a combination of NETA/EE and will report back to the Group at the next meeting.

5.1.4.7 The Group heard that skeletal variations had been observed with NETA/EE combinations in some studies in rodents and rabbits but considered these to be common occurrences that are not generally considered to be teratogenic. Furthermore, the available data could not rule out that that at such high doses the observed skeletal variations could be due to maternal toxicity.

5.1.5 ***Clinical pharmacology***

5.1.5.1 The Group considered the effects of Primodos in a small placebo-controlled randomised study in early human pregnancy in women seeking legal termination of pregnancy. This study found no difference between the groups in the pathology of the termination of pregnancy products that would be indicative of placental damage by Primodos.

5.1.5.2 The Group considered that it was difficult to prove a negative but that the study by Pulkkinen provides some reassurance that Primodos does not cause miscarriage through necrosis in the developing placenta; however, its power was too low to detect anything other than commonly occurring effects.

5.1.6 ***Overall conclusions***

5.1.6.1 Overall the Group considered that there were too many uncertainties in the data to support an estimation of how much EE and NETA the human placenta and/or fetus might have been exposed to following a maternal dose of Primodos and what effect this could have had.

5.1.6.2 The Group considered there to be no consistent picture across animal studies which would provide evidence of a clear biological mechanism or a signal for a teratogenic effect of NETA/EE, however the data could not

definitively rule out a causal association with non-genital congenital anomalies.

5.1.6.3 Nevertheless, on the basis of the non-clinical evidence presented the Group concluded that:

i. there was evidence of embryo-lethality in animal studies at high doses of NET/EE but the mechanism for this effect was not clear

ii. virilisation of the fetus could occur in association with NET but would require functional androgen receptor expression by the fetus and administration of NET at the right dose during organogenesis

iii. the skeletal variations observed in the animal studies could be explained by maternal toxicity at the doses tested

iv. there was no convincing evidence for a non-genital effect of NETA/EE on the fetus

5.1.6.4 The Group noted that vascular disruption had not yet been considered in detail as a potential mechanism for pregnancy loss and congenital anomalies in those who had been exposed to HPTs and suggested that this should be considered further.

6. Any Other Business

6.1 Mr Dobrik suggested that Professor David Healey's expertise could be helpful to the Group particularly in relation to the terms of reference around 'safeguarding future generations'. The Chair said that Professor Healey's expertise in ADRs had already been sought at the Group's second meeting but he should submit any additional evidence or information that may be valuable for the Group's discussions.

6.2 Mr Dobrik emphasised the importance of the work of the group in drawing lessons for the present regulatory system. The Group discussed the scope of this work and agreed that the terms of reference of the group which included consideration of any lessons for how drug safety issues in pregnancy are identified, assessed and communicated was sufficiently broad to capture this.

6.3 The Group commented that a critical evaluation of possible options and initiatives on pregnancy and congenital anomaly surveillance systems would be valuable in facilitating discussions relating to recommendations for the future. It was agreed that Drs Wellesley and Yates would present an options paper at the next meeting. Professor Price proposed that relevant experts on the Group could meet with the assessment team to be clear on their understanding of the available non-clinical data. She proposed that Ms Payne be present as an observer and also the Secretariat to ensure transparency.

Post meeting note: *a complete set of files containing all of the data that*

have been reviewed by the MHRA in their papers for the first three meetings has been made available to members, invited experts and observers of the HPTWG. This arrangement will continue with further progression of the review. This will allow the HPTWG to have sight of the data, negating the need for any separate meetings of experts of the HPTWG with the assessment team.

6.4 The Group emphasised the need for importance of clarity on the totality of available data in order that there could be confidence in the completeness of the review. MHRA agreed to provide the Group with an updated chronology and full schedule of available evidence to ensure no documents or evidence had been overlooked. MHRA also informed the Group that Dr Vargesson, a Cell Biologist at Aberdeen University, had been invited to present his work to the Group but, being unable to attend this meeting, would instead be asked to a future meeting.

7. Summary and meeting close

7.1 The next meeting date is **TBC.**

NOT FOR PUBLICATION

COMMISSION ON HUMAN MEDICINES

HORMONAL PREGNANCY TESTS WORKING GROUP

Minutes of the meeting held on Thursday 11th August 2016 at 10:00 in R-T-501-3, 5th floor, 151 Buckingham Palace Road, London SW1W 9SZ

Participants Present

Members

Dr A Gebbie (Chair)
Professor P Doyle
Mrs J Epstein
Professor Dr A Heep
*1 Professor S Hillier
*2 Professor A Macfarlane
*3 Ms S Payne
Professor S Price
Professor S Quenby
*4 Dr C Smith
*5 Professor M Threadgill
Dr D Wellesley *(presented item 5.3)*

Invited Experts

Mr N Dobrik
*6 Professor H Dolk *(presented item 5.3)*
Professor S Evans
Dr I Petersen
*7 Professor F Williams
*7 Dr L Yates

Observers

Mrs M Lyon
*8 PD Dr E Röhrdanz

Visiting Experts

Ms S Stevens *(presented item 5.3)*
Professor C de Vries *(presented item 5.4)*
Dr U Wandell Liminga *(presented item 5.4)*
Ms R Williams *(presented item 5.2)*

Professional Staff of MHRA Present

Supporting Specific Items	Item
Dr J Beynon (VRMM)	4
Dr K Ord (VRMM)	3.1 & 3.2
Dr S Seabroke (VRMM)	4

Observers

Mr M Dykes (COMMS)
Dr J Nooney (VRMM)
Mrs S Morgan (VRMM)
Dr J Raine (VRMM)
Dr J Woolley (VRMM)

*1 *arrived at 10:16 during item 1*
*2 *arrived at 10:14 during item 1*
*3 *left at 14:28 during item 5.4*
*4 *left during the lunch break (after item 5.3)*
*5 *left at 14:42 during item 5.4*
*6 *left at 15:24 during item 6*
*7 *arrived at 10:13 during item 1*
*8 *left at 15:06 during item 5.4*

15/10/16

Apologies
Professor L Aarons
Dr A Connolly
Mr I Currie
Professor J Harper
Professor K Marshall
Mrs F Pradhan
Dr R Quinton

Secretariat
Ms F Norris (Secretary)
Ms W Cheung

MHRA Legal
Ms K Foster *(10:00-13:00)*

1. Introduction and Announcements

1.1 The Chair reminded those present that the papers and proceedings are confidential and should not be disclosed and that all mobile phones must be switched off.

1.2 The Chair advised that:

Ms Rachael Williams
Research Statistician, Clinical Practice Research Datalink (CRPD)

would be attending as a Visiting Expert for item 5.2 - Using the Clinical Practice Research Datalink (CPRD) to collect data on medicines in pregnancy and congenital anomalies (presentation)

1.3 The Chair advised that:

Ms Sarah Stevens
Public Health Consultant at Public Health England, National Congenital Anomaly and Rare Disease Registration Service (NCARDRS)

would be attending as a Visiting Expert for item 5.3 - Future direction – registries of pregnancy and congenital anomalies (presentation)

1.4 The Chair advised that:

Dr Ulla Wandell Liminga
Scientific Director and PRAC delegate, Medical Products Agency, Sweden

and

Professor Corinne de Vries
Head of Science and Innovation Support (ad interim), European Medicines Agency

would be attending as Visiting Experts for item 5.4 - Good Vigilance Practice guidance (presentation)

1.5 Apologies were received from:

- **Professor Leon Aarons**
- **Dr Anne Connolly**
- **Mr Ian Currie**
- **Professor Joyce Harper**
- **Professor Kay Marshall**
- **Mrs Farrah Pradhan**
- **Dr Richard Quinton**

1.6 The Chair reminded those present to declare any personal interests (e.g. shares, lecture fees, consultancy, travel/accommodation costs or other direct remuneration) in the following associated companies:

Successors of the companies who originally marketed HPTs:

- Alinter Group
- Bayer plc
- GlaxoSmithKline UK
- Marshall's Pharmaceuticals Ltd
- Merck, Sharpe and Dohme Ltd
- Pfizer
- Piramal Healthcare Ltd
- Sanofi

The companies who originally marketed HPTs:

- Roussel Laboratories
- Parke Davis
- Wallace Manufacturing Chemists Ltd
- Schering
- Organon Laboratories
- Nicholas Laboratories Ltd
- Duncan Flockhart and Company Ltd.

The Chair reminded participants to declare the nature of any involvement they may have had with HPTs (e.g. reviews of these products, public commentary on their safety).

The Chair directed participants to **Tabled Paper I** – an updated list of the HPTWG declared interests.

The Chair advised that the following participants have declared additional information:

- **Dr Anne Connolly**: "I have personally received payment for lecturing, providing consultancy for and received travel and accommodation payments when attending conferences by Bayer PLC, MSD and Pfizer. These have all been unrelated to HPTs".

- **Professor Helen Dolk**: "I am a co-author of a paper published in 2016 considering the association between congenital anomaly risk and a range of medications used in pregnancy, including sex hormones. The data start in 1995, across Europe, and do not concern hormone pregnancy tests. Br J Clin Pharmacol. Given J et al. The Bayer grant to which I previously referred was for a 6 month period in 2010. As part of the EUROmediCAT project, we conducted a signal generation study looking for associations between specific congenital anomalies and any medications used during pregnancy, in data covering the period 1995-2011. This has recently been published (Given J, Loane M, Luteijn J, Morris J, de Jong-van den Berg L, Garne

E, Addor M-C, Barisic I, de Walle H, Gatt M, Klungsoyr K, Khoshnood B, Latos-Bielenska A, Nelen V, Neville A, O'Mahony M, Pierini A, Tucker D, Wiesel A and Dolk H (2016). EUROmediCAT Signal Detection: An Evaluation of Selected Congenital Anomaly-Medication Associations. British Journal of Clinical Pharmacology. DOI: 10.1111/bcp.12947). The medications examined did NOT include HPTS but included the contraceptive levonorgestrel/ethinylestradiol, pregnen (4) derivatives and pregnadien derivatives and synthetic ovulation stimulants. We are currently preparing to follow-up the results with more in depth study, again NOT in relation to HPTs for which we have no data".

- **Professor Siobhan Quenby**: "I received a fee for a lecture from Ferring".

- **Professor Faith Williams**: Professor Williams confirmed that the non-personal research funding for a member of staff in her team at Newcastle between 2004 and 2007 was from Pfizer.

The Chair advised participants that there was no change to the status of these participants in light of the new information declared.

Responses regarding updated interests have not yet been received from the following:

- Professor Joyce Harper

2. Minutes from the meeting held on Monday 25th April 2016

2.1 The minutes of the meeting held on Monday 25th April 2016 were adopted as a true and accurate record of the proceedings, subject to the clarification of Professor Evan's participation category.

3. Matters Arising

3.1 Updated schedule of information on HPTs

3.1.1 The Group noted that since it was first presented with a schedule of the documents that have been collated for the review in October 2015, further evidence has been received.

3.1.2 The Group noted that most of the additional evidence has been provided by Arnold and Porter LLP, who are the legal representatives for Bayer. The documents comprise information from litigation which was not already provided by other stakeholders and is not available from other sources.

3.1.3 The Group noted that the additional evidence includes: pre-clinical animal data from 23 studies; unpublished data from surveys and studies; clinical trials of Primodos and related clinical information; data from pharmacokinetic studies; base data from a number of published epidemiology studies; a

report on possible mechanisms; and a study of sales of HPTs and congenital malformations.

3.1.4 The Group also noted that a further 3 files had been provided by the Chair of the Association for Children damaged by HPTs, comprising largely correspondence between a number of different stakeholders, information regarding changes to Primodos package inserts and marketing of Primodos in various countries, and a summary of a non-clinical study.

3.1.5 The Group was assured that all new scientific data received from either source will be included in future papers to the Group.

3.1.6 The Chair asked for Mrs Lyon's input and gave her the opportunity to comment.

3.2 Updated usage of HPT products and chronology of events

3.2.1 The Group noted that the chronology of events (initially presented in October 2015) had been updated to include information provided by the former and current Chairs of the Association for Children Damaged by HPTs.

3.2.2 The Group noted that additional usage data had been provided by Arnold and Porter LLP in the form of a report entitled '"a study of sales of HPTs and congenital malformations" and the information on usage of HPTs from this report had been incorporated into the chronology of events.

3.2.3 The Group noted that the total number of prescriptions (unclear if issued or dispensed) for HPTs between 1966 and 1978 was estimated at 4.6 million, though this figure included their use in secondary amenorrhoea as well as diagnosis of pregnancy; sales data from 1959-1965 suggested additional use of HPTs during this period but no prescription data were available to confirm exact figures.

3.2.4 The Chair asked for Mrs Lyon's input and gave her the opportunity to comment. Mrs Lyon expressed concern that the data were flawed because they were obtained from a company that had links to Schering's legal representatives and was therefore not independent.

4. Paper

4.1 Further analysis of spontaneous reports with Hormone Pregnancy Tests

4.1.1 The Group noted the further work done by MHRA to address its request for further analysis of the spontaneously-reported adverse drug reaction data that had initially been presented to the Group in December 2015.

4.1.2 The Group noted that it had not been possible to obtain further details of litigation cases and therefore to identify any overlap between litigation cases and the cases provided by the Association for Children Damaged by HPTs.

4.1.3 The Group noted that verbatim terms from 227 HPT reports received by MHRA from various sources had been mapped to the World Health Organization ICD10 medical classification system, with the most commonly reported ICD10 chapters being "Congenital malformations, deformations and chromosomal abnormalities" (76% of all reports), "Mental and behavioural disorders" (19%) and "Diseases of the nervous system"(19%).

4.1.4 The Group noted that too few cases provided information on dose to obtain any useful information regarding a possible dose effect. Where timing of exposure was reported the anomaly coincided with the critical period of exposure as is expected, given that these products were commonly taken about 4-6 weeks after last menstrual period. A slight imbalance in type of anomaly reported and fetal gender was observed but numbers of cases were small.

4.1.5 The Group further noted that the most commonly reported anomalies fell within the ICD10 block Q65-Q79 'Congenital malformations and deformations of the musculoskeletal system' (36.1% of reports). When examining the extent to which events in different musculoskeletal blocks were co-reported, events were spread out with no observable pattern or clustering. Similarly, the types of musculoskeletal events reported within the overarching musculoskeletal system block were diverse, with 65% of reports describing only 1 event from within this block.

4.1.6 The proportion of all MHRA reports (from 1963-2016) describing musculoskeletal effects was approximately twice that of reports describing congenital heart defects. In contrast, the BINOCAR dataset (2012) and the Eurocat dataset (2008-2012) showed that congenital heart defects were reported more commonly than limb defects, as a proportion of all anomalies. The Group noted that when the MHRA data was broken down by period of reporting, musculoskeletal defects were reported more frequently than congenital defects from 1963 until 2006, after which the results changed to mirror those of BINOCAR/Eurocat with congenital anomalies being reported more frequently from 2006 to 2016. The Group considered that the preponderance of musculoskeletal defects in the early years of spontaneous reporting could be due to detection bias since musculoskeletal defects are more obvious at birth than heart defects, especially for stillbirths where a post mortem may not have been offered until more recent years.

4.1.7 The Group discussed the findings and emphasised that it may be useful to consider specific defects rather than broader anomaly groups, and focus on the specific types of anomaly reported in studies of HPTs (e.g. limb reductions defects, cleft lip/palate and neural tube defects). The Group also discussed whether it could be useful to classify ADR data according to the EUROCAT/BINOCAR system, and to consider extending the proportional analysis done for the musculoskeletal defects to other System Organ Classes. The Group commented on the importance of including data on stillbirths and miscarriages in analyses and of clarifying which statistical

methods had been applied to the spontaneous data (qualitative methods were used). In addition a disproportionality analysis and/or logistic regression of the ADR data by calendar year, defect and gender could be informative.

The Group went on to discuss the limitations of historical spontaneously-reported ADR data, the relatively small number of cases, the fact that nothing "stands out" from the data as a signal and the potential futility of attempting to dissect detail from minimally robust information to try and establish cause and effect.

4.1.8 The Group discussed whether ADRs caused by a genetic defect could be eliminated from the dataset and whether it would be helpful to phenotype the limb defects of members of the Association, ultimately deciding that this may not be as informative as conducting modern genetic testing of the individuals. The Chair requested that a scoping paper on genetic testing be brought back to the next meeting of the Group.

4.1.9 The Chair asked for Mrs Lyon's input and gave her the opportunity to comment. Mrs Lyon commented that data from 4-500 patients in Germany had not been included in the analysis and was informed that the absence of case-level information in these cases precluded their inclusion.

5. Presentations on data capture in pregnancy

5.1 Current position and options for registries in pregnancy and congenital anomalies (presentation/paper II)

5.1.1 Dr Wellesley presented information to the Group on Congenital Anomaly Registration in the UK. The Group noted that the British (Isles) and Irish Network of Congenital Anomaly Registers (BINOCAR) had been active since 1996 (and prior to this, since 1964 passive data collection NCAS had taken place). Since 2010 NCAS had ceased to collect data and registries have been put together more formally, with BINOCAR now providing data for the ONS. In England these databases covered 40% population, but the data collected was considered good quality and representative of the UK population.

5.1.2 The Group noted that data was collected from multiple sources, but midwives and paediatricians mostly reported (voluntarily) to the Registries, which collected data on livebirths and stillbirths, demographics, medical history, pregnancy and postnatal findings.

5.1.3 The Group noted the historical limitations of the Registries, including lack of accurate data on medication use, but noted that the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS) had taken over the management of the Registry and was aiming to link with prescription data in future, with data becoming available in the next year or two.

5.1.4 Professor Dolk presented information to the Group on Pharmacovigilance for medication safety in pregnancy, including data sources and designs. The Group noted the lack of information about use of medicines in pregnancy from clinical trials, the vulnerability of the fetus during gestation, and the relative rarity of adverse pregnancy outcomes (and the advantages of data collection through registries in this scenario). The Group noted the requirements for adequate pharmacovigilance in pregnancy, including a large population size, the ability to identify pregnancies, data on pregnancy outcomes, data on exposure to medicines during pregnancy, and information on lifestyle and socioeconomic factors.

5.1.5 The Group noted the various data sources, and the strengths and limitations of these, and particularly the limitations of 'pregnancy registries' with respect to inadequate sample size, loss to follow-up, poor recording of outcomes, lack of comparators, potential for duplication and the fact they are not population-based. The Group also noted the many limitations associated with spontaneous reporting data for pregnancy outcomes.

5.1.6 The Group noted the variety of approaches to pharmacovigilance, including case reports, cohort studies (and the sample sizes which would be needed for these), case-control studies and 'ecological' studies. The Group noted that ideally in future a multifaceted system could co-ordinate all available data sources and designs in phased pharmacovigilance, that special notifications for rapid assessment of high-risk products would be possible, that data linkage would be present, and data would be validated using human expertise.

5.1.7 The Group discussed the ways in which investigations of the use of medicines in pregnancy may be commissioned, and that researchers usually were able to access data but not be in receipt of it. The Group recognised the limitations of using historical data to conduct research due to incomplete data capture on anomalies, the lack of collaboration between existing data sources, threats to future research posed by difficulties in agreeing data linkage, and delays in identifying anomalies using existing registries.

5.1.8 The Chair asked for Mrs Lyon's input and gave her the opportunity to comment.

5.2 Using the Clinical Practice Research Datalink (CPRD) to collect data on medicines in pregnancy and congenital anomalies (presentation) - Ms R Williams

5.2.1 The Group noted the key features of the Clinical Practice Research datalink (CPRD), which covers England, Scotland, Wales and N Ireland, spanning a period of 28 years of data collection. The Group noted that CPRD includes primary care data on drug exposure, diagnoses and symptoms, referrals, laboratory tests, vaccination history, and demographic data. Patient identifiers are removed at source and the data are linked to other healthcare data.

5.2.2 The Group noted that GP practices opt in to CPRD while patients could opt out, and individual consent was required for patient reported outcome measures. Access to CPRD data was approved by an independent scientific advisory committee and could only be used for public health research.

5.2.3 The Group noted that CPRD could be used to study use of medicines in pregnancy, but there were challenges in identifying mother-baby pairs (for which an algorithm had been developed), and all pregnancies and outcomes. The Group noted that the latest version of CPRD had data on 1.1 million mother-baby pairs and ~780,000 mothers (between 10,000 and 53,000 pairs per calendar year).

5.2.4 The Group noted that the CPRD mother-baby link only looked at live births and mothers were only included if there was a link established; pregnancies with other outcomes (including stillbirths and miscarriages) were not included and no details on the pregnancies were captured, such as conception date, trimester dating, pre-term/post-term births, gestational age at outcome or multiple pregnancies. However, the Group noted the ongoing collaboration with the [redacted].

5.2.5 When questioned as to whether the MHRA used data on anti-epileptic drugs and exposure in pregnancy the Group was informed that research was sometimes hampered by data capture on only a limited number of patients, which made it difficult to address questions about safety with confidence, but efforts were being made to expand coverage.

5.2.6 The Chair asked for Mrs Lyon's input and gave her the opportunity to comment.

5.3 Future direction – registries of pregnancy and congenital anomalies (presentation) - Ms S Stevens

5.3.1 The Group was provided with background information about Public Health England (PHE)The Group noted that it was within the remit of PHE to ensure nationwide coverage of the congenital anomaly register (NCARDRSR) and was informed of the progress made by PHE in developing and running the national congenital anomaly and rare disease registration service for England.

5.3.2 The Group noted that the registry was covered across a number of local authority districts, with data (both paper and electronic) collected from both regional and national sources in the antenatal setting, in newborns and in children and adults; Reporting was not mandatory and most notifications came neonatally or antenatally from secondary care.(predominantly midwives and paediatricians).

5.3.3 The Group noted that legacy data migration was aimed to be complete by September 2016 and the intention was to get two-way data sharing agreements in place; the registry would output to International sources

(EUROCAT, Orphanet), and National and regional/local stakeholders. The group noted that NCARDRSR had close links with genomics, fulfils commitments made within the UK strategy for rare diseases and there was European and International interoperability.

5.3.4 The Group raised the issue of whether notification should be mandatory, recognising this would require government involvement, and the ability to opt-out (though it was confirmed that no requests to opt out had been received in the last 18 months). The group also discussed how the data could be used for research purposes, noting that at present the registry was collecting data only with no plans for analysis, although there was some small analytical capacity within the Registry team, which may need to be expanded.

5.4 Good Vigilance Practice guidance (presentation) - Dr U Wandel-Liminga and Professor C de Vries

5.4.1 Dr Wandel-Liminga provided the Group with an overview of the concepts underpinning the Good Pharmacovigilance Practice module on pregnancy and lactation (in development), with a particular focus on the Risk minimisation and Pharmacovigilance aspects.

5.4.2 The Group was informed of the existing guidance on medicines in pregnancy and lactation, including:

- Guideline on risk assessment of medicinal products on human reproduction and lactation: From data to labelling;
- Guideline on Exposure of medicinal products during pregnancy: Need for post-authorisation data;
- Guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals;
- Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility;
- Recommendations related to contraception and pregnancy testing in clinical trials.

5.4.3 [redacted]

5.4.4 The Group was informed of the challenges regarding: unintended exposures; masked outcomes/competing endpoints; sample size considerations; delayed effects (long after birth/long after marketing); typical biases in this area of medicine safety evaluation; timing of exposure; class effects; communication of risk; and effective implementation of risk minimisation measures in practice.

5.4.5 [redacted]

5.4.6 The Group was informed about a real-life recent example of risk minimisation for the use of thalidomide in multiple myeloma, comprising both routine and additional risk minimisation (i.e. controlled distribution systems, a pregnancy prevention program, pregnancy reporting requirements and treatment initiation forms including confirmation that the physician has talked to patient regarding a number of points).

5.4.7 Professor de Vries provided the Group with a summary on the progress made with drafting of the Good Pharmacovigilance Practice (GVP) module on pregnancy and lactation, the driving principle of which was the determination of changes to the balance of risks and benefits of a medicine given the introduction of the fetus as a 'third party'.

5.4.8 [redacted]

5.4.9 The Group noted the variety of data sources for drug safety in pregnancy evaluation, including several pregnancy registries and population-based record linkage surveillance systems. [redacted]

5.4.10 [redacted]

5.4.11 [redacted]

[redacted]

5.4.12 The Chair asked for Mrs Lyon's input and gave her the opportunity to comment. Mrs Lyon commented that Sweden was one of the first countries to ban Primodos, and requested further information. Dr Wandel-Liminga confirmed she would try to find out more and report back to the MHRA.

5.4.13 [redacted]

5.4.14 It was suggested that miscarriage rate was the biggest detector of harm during pregnancy and it would be important to cover this in the Module. Dr Wandel-Liminga stated that it would be useful to obtain data on miscarriages in animals, as these are a good predictor of outcomes in humans, but highlighted the difficulties (in Sweden) of collecting data on miscarriage or elective abortion.

5.4.15 Other comments made included the need for very large databases because most pregnancies have healthy outcomes, the need to collect data on drug exposure and possible confounders prior to conception and at a very early stage of pregnancy, with good follow-up.

6. Any Other Business

6.1 Participants raised the following additional points:

- Ideally there should be a central co-ordinating body to oversee research on medicines in pregnancy, which should be properly funded
- Rather than look to the past it is important to be forward-looking with respect to how to minimise the risk of congenital anomalies in future and focus efforts on this as the Group reaches its conclusions
- The need to be mindful of data protection issues and what the implications may be for future research
- There are more studies which need to be evaluated; documents have allegedly shown that William Inman suggested a 5:1 risk of malformations with Primodos. MHRA agreed to try to locate these documents.

6.2 MHRA clarified that the next meeting of the Group would include: an update on non-clinical data (to include studies from Bayer); a presentation from Dr N Vargesson; a paper on vascular disruption; and epidemiological evidence on HPTs and any effect on early pregnancy.

6.3 The Group noted that Dr Vargesson had previously published a study on zebrafish/chick embryos, and commented that it would be helpful to see his study data in advance of the meeting.

7. Date and Time of Next Meeting

7.1 Tuesday 18th October 2016 at 10am.

NOT FOR PUBLICATION

COMMISSION ON HUMAN MEDICINES

HORMONAL PREGNANCY TESTS WORKING GROUP

Minutes of the meeting held on Tuesday 18th October 2016 at 10:00 in R-T-501-3, 5th floor, 151 Buckingham Palace Road, London SW1W 9SZ

Participants Present

Members

Dr A Gebbie (Chair)
Professor P Doyle
Mrs J Epstein
*1 Professor S Evans
Professor J Harper
Professor Dr A Heep
Professor S Hillier
*2 Professor A MacFarlane
*3 Ms S Payne
*4 Mrs F Pradhan
Professor S Price
*5 Dr R Quinton
Dr C Smith
Professor M Threadgill
Dr D Wellesley (presented item 5.2)

Invited Experts

*6 Mr N Dobrik
*6 Professor H Dolk
*6 Professor K Marshall
*7 Dr I Petersen
*8 Professor F Williams
*9 Dr L Yates

Observers

*6 Mrs M Lyon
*6 PD Dr E Röhrdanz

Visiting Experts

Dr N Vargesson (item 6.1 only)

Professional Staff of MHRA Present

Supporting Specific Items	Item
Dr J Beynon	5.1
Mr J Clements	6.2
Mrs P Datta-Nemdharri	4.1
*10 Dr M Harrison-Woolrych	4.1
Dr J Nooney	7.1
Dr S Seabroke	4.1
Dr J Woolley	5.2, 9

Observers

Dr K Ord
Mr N Spears
Dr J Raine

*1 *via teleconference between 10:09-11:27 during item 4*
*2 *arrived at 10:08 during item 1; left at 17:17 during item 9*
*3 *left at 14:25 after item 6.1*
*4 *left at 15:55 after item 8*
*5 *arrived at 11:20 during item 4.1, left at 15:55 after item 8*
*6 *left after item 8*
*7 *left at 16:02 after item 8*
*8 *via teleconference at 12:42 during item 5.2 until 13:55 (lunch break); re-joined at 14:31 during item 6.2 until 16:40 after item 8*
*9 *via teleconference from 10:01 until 13:55 (lunch break); re-joined at 14:36 during item 6.2, left at 16:40 after item 8*
*10 *via teleconference for item 4.1*

27/3/17

Apologies
Professor L Aarons
Dr A Connolly
Mr I Currie
Professor S Quenby

Secretariat
Ms F Norris (Secretary)

MHRA Legal
Ms K Foster *(in person 10:00-16:15, via teleconference 16:17-16:41)*

1. Introduction and Announcements

1.1 The Chair reminded those present that the papers and proceedings are confidential and should not be disclosed and that all mobile phones must be switched off.

1.2 The Chair advised that:

Dr Neil Vargesson BSc (Hons) Ph.D. FHEA
Senior Lecturer, School of Medicine, University of Aberdeen

would be attending as a Visiting Expert for item 6.1.

1.3 Apologies were received from:

- Professor Leon Aarons
- Dr Anne Connolly
- Mr Ian Currie
- Professor Siobhan Quenby

1.4 The Chair reminded those present to declare any personal interests (e.g. shares, lecture fees, consultancy, travel/accommodation costs or other direct remuneration) in the following associated companies:

Successors of the companies who originally marketed HPTs:

- Alinter Group
- Bayer plc
- GlaxoSmithKline UK
- Marshall's Pharmaceuticals Ltd
- Merck, Sharpe and Dohme Ltd
- Pfizer
- Piramal Healthcare Ltd
- Sanofi

The companies who originally marketed HPTs:

- Roussel Laboratories
- Parke Davis
- Wallace Manufacturing Chemists Ltd
- Schering
- Organon Laboratories
- Nicholas Laboratories Ltd
- Duncan Flockhart and Company Ltd.

The Chair reminded participants to declare the nature of any involvement they may have had with HPTs (e.g. reviews of these products, public commentary on their safety).

The Chair directed participants to **Tabled Paper I** – an updated list of the HPTWG declared interests.

The Chair advised of the following:

Professor Harper:
Professor Harper has now returned the confidentiality and conflict of interest agreement form. She has no other information to add to her original declaration of no interests.

Dr Yates:
Dr Yates has provided clarification on her declaration. She advised: "I can confirm that the information on our 'bumps' website is in essence a summary of what UKTIS produced for Professor Robson, and which I informed the MHRA of at an early stage. I received no personal remuneration for the work. A fixed fee was paid to UKTIS to undertake the work, but was less than the 'true' cost the report - if the staff time spent is used to calculate the cost, and could therefore be seen as having a part- voluntary contribution which is reflected in the unpaid/uncompensated overtime that members of UKTIS provide (of their own volition) on a regular basis".

Professor Dolk:
Professor Dolk wished to update her declaration, which introduces no new information except that Euromedicat was funded by EU FP7. She advised: "My institution (Ulster University) has had a recent research grant from GlaxoSmithKline UK ending in March 2014, on the subject of antiepileptic drug safety in pregnancy. I was the principal investigator. For a 6 month period in 2010, I was co-investigator on a project regarding maternal age and neural tube defects funded by Bayer. Funding again went to Ulster University as a research grant. I have no personal interests in any of the companies listed. As part of the EUROmediCAT project, funded by EU FP7, we conducted a signal generation study looking for associations between specific congenital anomalies and any medications used during pregnancy, in data covering the period 1995-2011. This has recently been published (Given J, Loane M, Luteijn J, Morris J, de Jong-van den Berg L, Garne E, Addor M-C, Barisic I, de Walle H, Gatt M, Klungsoyr K, Khoshnood B, Latos-Bielenska A, Nelen V, Neville A, O'Mahony M, Pierini A, Tucker D, Wiesel A and Dolk H (2016). EUROmediCAT Signal Detection: An Evaluation of Selected Congenital Anomaly-Medication Associations. British Journal of Clinical Pharmacology. DOI: 10.1111/bcp.12947). The medications examined did NOT include HPTS but included the contraceptive levonorgestrel/ethinylestradiol, pregnen (4) derivatives and pregnadien derivatives and synthetic ovulation stimulants. We are currently preparing to follow-up the results with more in depth study, again NOT in relation to HPTs for which we have no data".

The Chair advised participants that there was no change to the status of these participants in light of the new information declared.

Professor Stephen Evans:

At the meeting in August, during the discussion of the minutes of April's meeting, Professor Evans queried his participation category of Invited Expert and whether he should in fact be a full Member. Professor Evans has since provided the following clarification: "As far as I know, GSK have at least a year ago, ceased paying any money to LSHTM for Medical Statistics. I think that, like Pat Doyle, I do not have any financial interests in any pharmaceutical company".

It has therefore been agreed that Professor Evans should be moved to the Member category. This change will be in effect from today's meeting.

2. Minutes from the meeting held on Thursday 11th August 2016

2.1 The Group discussed the minutes of the meeting held on 11th August 2016. Mrs Lyon questioned part of the minutes relating to historical usage data, in particular the statement "data may be best that could be obtained given the passage of time". It was agreed while this was a factual statement it would be removed from the final minutes, which were otherwise agreed.

3. Matters Arising

3.1 Debate in the House of Commons on 13th October 2016

3.1.1 The Chair raised the issue of the debate on HPTs which took place in the House of Commons on 13/10/2016, a transcript of which had been provided to the Group. The Chair asked that anyone contacted by the media as a result of this debate, should refer queries to the MHRA Press Office.

3.1.2 The Group expressed their concerns about the debate and the accuracy of many of the statements made. One particular issue related to the information on HPTs on the UK Teratology Information Service (UKTIS) 'BUMPs' website and Dr Yates' involvement in the EWG review given these clear 'conflicts of interest'. Dr Yates explained that the statements that had been made in the debate regarding her personal involvement with the information on the websites and their conclusion with respect to HPTs and congenital anomalies were inaccurate. Dr Yates clarified the context of both issues and confirmed that all conflicts of interest had been fully declared.

3.1.3 The Group were concerned about the statements made in the debate which implied that a causal association between HPTs and birth defects was proven, and was concerned that such messages could undermine the work of the Group.

3.1.4 On a personal level, very public and inaccurate criticism of the Group's integrity and expertise was of concern to individual members and was considered a threat to the recruitment of experts to future expert working groups. Additional comments on the debate were taken as AOB.

3.1.5 ***Post meeting note:*** *In light of the concern, a clarifying statement has been added to the BUMPS and UKTIS websites.*

4. Review of the epidemiological evidence

4.1 Epidemiological evidence for a possible association between norethisterone and ethinylestradiol and an adverse outcome in early pregnancy (MHRA Paper 3)

4.1.1 The Group was presented with a summary of the epidemiological evidence relating to use of: 1) HPTs and congenital anomalies, 2) oral contraceptives (OCs) and congenital anomalies, 3) norethisterone acetate (NETA) to sustain pregnancy in women with threatened or recurrent miscarriage and congenital anomalies, and 4) ethinylestradiol (EE) and/or NETA (for any indication) and miscarriage.

4.1.2 Evidence assessed during the review included: published literature on EE and/or NETA, published and unpublished evidence submitted by Bayer, and hand-searching of reference lists identified from the first two steps. No language or date restrictions were applied and search terms related to adverse pregnancy outcomes (according to the EUROCAT Description of Congenital Anomaly Subgroups) and miscarriage. Over 6,000 publications were identified and were screened for relevance, applying strict inclusion and exclusion criteria; where necessary, foreign language papers were professionally translated. Exclusion criteria were clearly defined in advance and included: i) non-epidemiological data (passed on to the relevant assessor); ii) no data on birth defects or miscarriage; iii) no data on exposure during pregnancy; iv) studies examining chromosomal disorders; and v) use of female sex hormones for a different indication/study population.

4.1.3 The Group noted that virilisation was not examined in the review because it is a known effect of the androgenic properties of NETA.

4.1.4 The Group noted the limitations of much of the data that were perceived at time(s) of publication and that later studies attempted to address at least some of these concerns. Where possible studies were categorised and reviewed by major anomaly.

4.1.5 a) HPTs and congenital anomalies

4.1.5.1 The Group noted that of 4390 publications initially identified, 175 papers were assessed in more detail and a further 78 excluded, to leave 97 papers that were evaluated in full. Nineteen papers were translated from foreign languages.

4.1.5.2 The Group noted there to be very little literature with NETA/EE use as an HPT specifically; however some individual studies warranted further detailed examination. In particular, the Spanish Registry study, which found a very high relative risk of congenital anomalies in general, was of greater concern than some other studies and it would be important to look in greater detail at the robustness of the study. With respect to congenital heart defects and

neural tube defects in particular, the Group considered that the evidence for no association was not so clear-cut as for other defects and so it would be important to re-evaluate the relevant studies in terms of their robustness. The Group noted that more positive associations were observed in studies of limb reduction defects than in studies of limb defects generally and these should be evaluated separately.

4.1.5.3 The Group recognised the difficulties in assessing the available studies on HPTs due to their dated methodology and the significant changes that had since occurred within the field of epidemiology. The Group noted that applying current scientific rigour as inclusion/exclusion criteria for further assessment would exclude the majority of the studies. The Group therefore considered that it would be important to re-analyse the evidence using a formal quality scoring system that assessed all studies according to a pre-defined set of quality criteria. These could be scored using a traffic light scale of green/amber/red (where green indicated good quality, amber moderate and red poor quality) with the data presented using Forest plots. Where possible: odds ratios should be calculated from proportions data, absolute rates and numbers of events should be provided; cohort studies should be presented separately from case-control studies; and studies of limb reduction defects should be presented separately from studies of all limb defects. The Group advised that, if possible, it would also be of interest to stratify by timing of administration of HPT relative to organogenesis, by funding (industry vs non-industry) and by geographical location (UK vs US vs EU).

4.1.6 b) OCs in pregnancy and congenital anomalies

4.1.6.1 The Group noted that of 1480 publications initially identified 251 were assessed in more detail and a further 165 excluded, to leave 86 papers that were evaluated in full. The Group was presented with a summary of the study findings, grouped by major anomaly, and the perceived strengths and limitations of each study.

4.1.6.2 The Group considered that review of a significant body of evidence of OCs taken inadvertently in pregnancy (>11,000 exposed women) had not found any association between OC use and an increased risk of limb deformities, congenital heart defects (including cono-truncal anomalies), urogenital anomalies, neural tube defects and anomalies generally. For other specific cardiovascular defects, for example hypoplastic left heart syndrome, the data were limited due to the rarity of such anomalies. For VACTERL (vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities) and EFESSE Syndrome the available evidence is also limited but does not support an association with OC exposure during pregnancy.

4.1.6.3 The Group stated that the findings should provide important reassurance for millions of women who take these products, especially given the 8% failure rate of OCs.

4.1.7 c) NETA and/or EE in women with threatened or recurrent miscarriage and risk of congenital anomaly

4.1.7.1 The Group noted that of 405 publications initially identified 99 were assessed in more detail and a further 65 excluded, to leave 34 papers that were evaluated in full. The Group noted that all studies had limitations and few were considered to be of good quality. More recently-published studies tended to be more robust but lacked information on the exposures of interests. Of the 8 studies that specified that NETA had been used, 3 reported an association and 5 reported no association with congenital anomalies.

4.1.7.2 The Group noted that studying congenital anomalies in the indication threatened or recurrent abortion was complicated □ many study authors pointed out that treatment with a progestogen may prolong a pregnancy with a malformed baby (which may otherwise have failed). The Group noted that where relative risks were presented, these ranged broadly from low (1.5) to high (6), and had very wide confidence intervals. Overall the Group considered there was little evidence of significant harm in association with OC use in early pregnancy.

4.1.8 d) NETA/EE in early pregnancy and risk of miscarriage

4.1.8.1 The Group noted that much of the information relating to the use of NETA/EE to induce miscarriage was anecdotal. The literature search initially identified 405 publications, of which 47 were reviewed in more detail and a further 26 excluded, leaving 26 papers that were evaluated in full (12 papers were translated from foreign languages). Four studies were based on the use of hormones as HPTs, two of which described use of NETA/EE specifically. All miscarriage rates for women exposed to sex hormones in the studies were within the background range of 5-20% published elsewhere. Regarding exposure to NETA for other gynaecological indications, 11 studies were identified, of which 9 reported rates of miscarriage within published/accepted ranges. One small case series and one small cohort study reported higher miscarriage rates among NETA-treated pregnancies.

4.1.8.2 The Group considered that overall, scientific evidence for an abortifacient effect of either EE or NETA administered during early pregnancy was sparse, and the majority of studies did not provide evidence for a causal association between EE and/or NETA and miscarriage.

4.1.8.3 On the basis of the totality of the epidemiological evidence presented the Group commented that there was no obvious consistent pattern for a particular or specific adverse outcome and, overall, there was little evidence for an association between EE/NETA and adverse outcomes in pregnancy. Nevertheless, before a firm conclusion could be drawn it would be important to re-evaluate the studies relating to the use of EE/NETA to diagnose pregnancy as described above.

4.1.8.4 Refer to item 9 for final conclusions and recommendations.

5. Matters Arising

5.1 Further ADR analysis and disproportionality paper from UKTIS (Work Plan)

5.1.1 The Group noted Tabled Paper II.

5.1.2 The Chair asked participants to note Tabled Paper II, with written comments on the ADR work plan from Professors Evans, Dolk and Doyle, and Dr Yates.

5.1.3 The Group was informed that the ADR work plan proposed further analyses of spontaneously-reported ADR data for HPTs. The Group noted that 'spontaneous data' included Yellow Cards and cases received from the Association and other sources.

5.1.4 The Group accepted that the further analyses of spontaneous reporting would be unlikely to enable a definitive conclusion to be drawn, however it may provide further information about patterns of reported abnormalities and it was important that every effort was made to examine the ADR data as comprehensively as possible.

5.1.5 Mrs Lyon was invited to speak and had no comments to add.

5.2 Genetic testing scoping paper

5.2.1 The Group considered a scoping paper looking at the possibility of offering full genetic testing to members of the Association (or their offspring) with a congenital anomaly. Exact details of this will be decided in due course. The first step in the process would involve offering Chromosome MicroArray assessment to identify a chromosomal error. Those with a negative finding could have a consultation with a Clinical Geneticist to exclude known non-genetic conditions. Those with a negative result and, where possible, both their parents could then be offered whole exome sequencing. Approximate timings and costs for each stage of testing were presented to the Group; depending on the findings of the test at each stage this would be expected to take between 4 and 36 weeks to complete per individual.

5.2.2 The Group noted that changes to the exome or genome would be detected through genetic testing but that epigenetic changes (heritable traits, or "phenotypes") that could not be explained by changes in DNA sequence would not.

5.2.3 The Group noted that genetic testing could not prove or disprove an association between congenital anomalies and use of HPTs – it could only exclude known genetic or other causes. If agreed as a possible option, the Group could send a letter to local geneticists, who could feedback to the Group, subject to the agreement of the individuals tested.

5.2.4 Once all phenotypic data had been collected from geneticists it might be possible to focus on groups of malformations (e.g. heart defects). The Group noted that it was not possible to say what proportion of malformations are genetically linked and that individuals would need to be assessed to see if a more multi-systemic effect was evident.

5.2.5 Mrs Lyon was invited to speak and had no comments to add.

5.2.6 Refer to item 9 for final conclusions and recommendations.

5.3 Translation of excerpts from Landesarchiv Berlin files

5.3.1 The Group noted Tabled Paper III (Excerpts from Landesarchiv Berlin files, translated by Prof Dr Axel Heep). This was provided in response to a statement made by Mrs Lyon at the previous meeting regarding a 5-fold increase in risk of malformations informally communicated by Dr Inman to Schering in 1975.

5.3.2 The Group noted excerpts from the archives stating that "Drug monitoring in pregnancy over the last five years has shown, that among those who had had a hormonal pregnancy test, there is a relative risk of 5:1 in having a deformed child. The investigation is not yet entirely completed, it is to be expected that within the next six months, a corresponding publication will be published." These levels of risk correspond with those observed in the CSM's interim study report (Greenberg et al 1975).

5.3.3 Mrs Lyon stated that she was unhappy about some of the comments made during the discussion and asked that these documents be made available for the Group's scrutiny.

5.3.4 ***Post meeting note****: all translations from the Landesarchiv Berlin were sent to the Group on 20th February 2017 for consideration at the meeting of the Group on 24th April 2017.*

6. <u>Review of pre-clinical data</u>

6.1 New pre-clinical data on the effects of HPTs - Presentation by Dr Neil Vargesson, Senior Lecturer, School of Medicine, University of Aberdeen

6.1.1 Dr Vargesson informed the MHRA in advance that his presentation would last 20-25 minutes. Copies of the slides were not provided. The presentation contained photographic images of his research work.

6.1.2 Dr Vargesson presented preliminary findings from small studies looking into the effects of EE and NETA on blood vessel and limb development using zebrafish and chick embryo models, respectively. Dr Vargesson highlighted the need to keep the details of his findings confidential at this stage; however, the high level findings were for no developmental effects of NETA/EE on chick embryos, even at very high doses, and dose dependent

lethality in zebrafish embryos at high concentrations, with partially reversible effects on some developmental parameters.

6.1.3 Dr Vargesson confirmed he was preparing these data for publication and would be prepared to share the draft manuscript with the Group once submitted.

6.1.4 The Group asked Dr Vargesson a number of questions regarding his research and methodology. Dr Vargesson said he would take these points into consideration in further work.

6.1.5 Refer to item 9 for final conclusions and recommendations.

6.2 Update on evidence from pre-clinical data relevant to a possible association between norethisterone and ethinylestradiol and adverse effects on pregnancy or the developing fetus (MHRA Paper 1)

6.2.1 A review of the available non-clinical data was first presented to the Group at their third meeting. This updated review additionally took into consideration 24 reproductive toxicity studies conducted by Schering (the MAH for Primodos) and obtained from Arnold and Porter LLP.

6.2.2 The Group considered the new data in the context of the totality of the available evidence. The Group noted that embryo-lethality was observed with high doses of EE across a range of species. The Group also noted that there was evidence of changes in fetal reproductive tissue with EE in some studies and that similar effects on embryolethality and fetal reproductive tissue have been observed with NETA. The Group noted that the virilising effects of NETA on female fetuses were related to its known androgenic activity and could occur if exposure occurred during development of fetal reproductive tissue.

6.2.3 The Group noted that studies in which NETA/EE combinations were administered during the period of organogenesis in mice, rats, guinea pigs, rabbits and non-human primates had been performed. As with studies of NETA and EE alone, combinations of NETA/EE administered during early pregnancy increased the incidence of embryo resorptions/abortions. The mechanism by which NETA/EE cause embryo loss was not established but sensitivity to this effect was species-specific. Data from non-human primates, the most physiologically relevant animal species, suggested a small increase in pregnancy loss at around the equivalent Primodos dose when given daily for 30 days during early pregnancy.

6.2.4 The Group noted that some mice studies found an association between embryolethal doses of NETA/EE given throughout organogenesis and an increase in thoracic malformations. In studies in rats, rabbits, and non-human primates no similar evidence of an increase in malformations was observed. The Group also noted data from rodents and rabbits that found an association between NETA/EE combinations and an increase in frequency of skeletal variations.

6.2.5 The Group commented that the historical nature of the studies together with the variety of routes and administration schedules studied made it difficult to interpret the findings. The Group considered that the data appeared to demonstrate a range of toxicities with NETA and/or EE, including embryo lethality and virilisation, which varied according to the species, dose, and administration schedule. The Group commented that all of these effects may be due to changing hormonal balance within the mother and the fetus. The Group thought that the 5 malformations that had been observed through special histological examination of mice in Schering study 3579 could have been related to the sensitivity of the mouse to the high oral dose of NETA/EE that was administered (250 times the equivalent human dose in Primodos or around 30-fold when estimated based on body surface area). When considering known teratogens, the Group commented that observations made in the mouse in isolation were not usually predictive of an effect in humans. Similar histological studies with NETA/EE in the rat did not reveal an increase in malformations. Nevertheless, it should be borne in mind that marked embryolethality could mask possible developmental effects, by giving rise to fewer evaluable fetuses.

6.2.6 The Group noted that rats were not sensitive to the teratogenic effects of thalidomide but in some studies could show an increase in resorptions. It was confirmed that chemical teratogens were typically identified in experimental animal models although as in the case of thalidomide there could be species specific differences.

6.2.7 It was questioned whether the findings of Schering study 2221, which showed substantial embryolethality at low doses, had been included in the review. MHRA confirmed that this study was included in the assessment report and related to the subcutaneous administration of estradiol benzoate and progesterone in rats (rather than oral administration of NETA/EE). It was considered that by avoiding first pass metabolism the subcutaneous route of administration would increase exposure and that the natural compounds may not necessarily be expected to have less effect than synthetic ones.

6.2.8 The Group commented that despite the limitations of the non-clinical data, no compelling signals for abnormalities associated with NETA and/or EE had been identified.

6.2.9 Refer to item 9 for final conclusions and recommendations.

7. Review of Vascular Disruption

7.1 Evidence for disruption of the vasculature of the developing pregnancy by Hormone Pregnancy Tests (MHRA Paper 2)

7.1.1 The Group considered a review of the evidence for vascular disruption during pregnancy as an indirect cause of congenital defects by NETA/EE. The review highlighted that historically disruption of the maternal blood supply,

disturbed blood supply within the placenta or disruption of the embryofetal vasculature or circulation, have been considered as possible indirect causes of congenital defects. The evidence was based on experimental disruption of vascular supply in animal studies, clinical observations of congenital anomalies with human twin pregnancies and exposure during early pregnancy to chorionic villus sampling or to unsuccessful misoprostol (off-label) use as an abortifacient. The Group noted vascular disruption could occur at any time during pregnancy, and could theoretically cause a range of anomalies depending on the site and timing of the disrupted vascular supply.

7.1.2 No citations to progestogens in general, or NETA in particular, as possible causes of vascular disruption were identified. However the Group noted that the review explored evidence for analogous mechanisms that might potentially occur with EE and/or NETA.

7.1.3 The Group noted that both progesterone withdrawal and the mifepristone (a progesterone antagonist) increase uterine tone and responsiveness to oxytocin and prostaglandins, and that reports of congenital anomalies following mifepristone use alone or in association with prostaglandins, had been published. However mifepristone has a different pharmacological profile to NETA and no studies of uterine tone or contraction patterns during exposure to EE and / or NETA had been identified.

7.1.4 The Group noted that acute reductions in uterine arterial blood flow, due to uterine artery vasoconstriction, had been proposed as a possible underlying mechanism for misoprostol-induced congenital abnormalities. Two small studies, one in women with premature ovarian failure and one in naturally post-menopausal women receiving hormone replacement therapy found that estradiol reduced uterine arterial vascular resistance and that NET increased vascular resistance compared to estradiol alone. However no studies of uterine arterial blood flow during exposure to EE and/or NETA to women with natural menstrual cycles or during pregnancy were identified, so any possible effect of EE/NETA on uterine arterial blood flow due to vasoconstriction in the presence of higher endogenous hormone levels remain unknown.

7.1.5 The Group noted that acute reductions in maternal uterine arterial blood flow could also occur due to formation of a blood clot; however, perfusion of the intervillous space of the placenta by maternal blood is considered to occur from the end of the first trimester onwards in most pregnancies and so this may be an unlikely mechanism.

7.1.6 Direct occlusion of embryofetal blood vessels could also occur due to an increased thrombotic risk in the fetus. The Group noted that coagulation proteins have been detected in the fetus from about 5 weeks of gestation and are expressed early and widely during embryonic and fetal development. At this stage of development these factors appeared to act as regulators of tissue proliferation and differentiation rather than as clotting factors.

7.1.7 The Group considered that the evidence reviewed illustrated that dose-related effects of sex hormones could lead to blockade of physiological

effect, but that it was difficult to understand how use of two doses of EE/NETA taken 12 hours apart could exert such an effect, particularly against a background of high levels of endogenous hormones. The Group commented that NETA is an anti-inflammatory steroid that interacts with the glucocorticoid receptor at certain doses and would be expected to have anti-disruptive rather than pro-disruptive effects during pregnancy.

7.1.8 Refer to item 9 for final conclusions and recommendations.

8. Any other Business

8.1 Apology from the Association for Children Damaged by Hormonal Pregnancy Tests

8.1.1 Mrs Lyon issued an apology on behalf of the Association for the way in which the Group had been referred to in the Westminster debate and clarified that members of the Association had contacted their MPs because of misunderstandings about the article on UKTIS/BUMPS and Dr Schaefer's involvement with the Group. Mrs Lyon also referred to the historical review on HPTs that was published on the MHRA website.

8.1.2 Mrs Lyon referred to a statement of apology she had prepared and provided a copy to Dr Gebbie (located at **Annex I**, page 19); the secretariat confirmed they would scan it (so the members of the EWG could be provided with a copy).

8.1.3 The MHRA press officer informed the Group that there had been some media coverage following the debate and that MHRA defends the committee robustly.

8.1.4 Mr Dobrik stated that he had no doubt the EWG review was being conducted appropriately, and needed to come to a conclusion based on all the evidence, including translations of the documents in the Landesarchiv Berlin (submitted by Mrs Lyon). To increase external confidence in the work of the Group Mr Dobrik suggested that these documents should be translated in full and provided to the Group. Mr Dobrik said it was regretful that members of the Association had been upset by the experience of presenting to the Group.

8.1.5 The Chair reminded the Group that the Association members who gave evidence at the December 2015 meeting had not been given any time limits and that it was important for members of the Association to have confidence in the work of the Group. Furthermore, it was important to reassure the Association that due process is being followed (whilst being fair to all parties) and that complete translations of the Landesarchiv Berlin documents will be provided to the Group.

8.2 Date of Next Meeting

8.2.1 The Chair informed the Group that a number of issues are scheduled for discussion at the next meeting, including further analyses of ADR data, re-analysis of the epidemiological data, and an update on valproate. A date for the next meeting would be confirmed and a draft agenda would be circulated in advance of the next meeting.

9. Meeting conclusions and recommendations - Advice sought (MHRA paper 4)

As per the participation definitions provided to the Group at the beginning of the review, Invited Experts and Observers are not permitted to contribute to conclusions and recommendations and so left the meeting at this point.

9.1 Genetic testing

9.1.1 The EWG Members discussed whether members of the Association for Children Damaged by Hormonal Pregnancy Tests should be offered genetic testing.

9.1.2 Members were advised that the issue of costs should not play any part in their decision-making which should be based solely on their scientific opinion.

9.1.3 The EWG Members discussed the need to be very sensitive to the potential impact on individuals of undergoing genetic testing, and potential for distress to an individual who receives a result they were not expecting.

9.1.4 The EWG Members were reminded that Mrs Lyon had previously confirmed that the Association would be content to be offered genetic testing.

9.1.5 The Members concluded that:

- genetic testing should be offered to members of the Association, with relevant information/counselling to enable them to decide whether they wanted to take up the offer
- testing should take place at local testing centres provided with background information on the context
- testing should be offered for the benefit of the members of the Association and not to inform the conclusions of the review.
- individuals would be free to feed the results back to the Group if wished.

9.2 Non-clinical evidence

9.2.1 EWG Members considered the available evidence on non-clinical findings and advised that:

1. Norethisterone acetate and ethinylestradiol when administered singly

or in combination in rodents, rabbits and non-human primates during early pregnancy increased the incidence of embryo resorptions/abortions.

2. The mechanisms of embryo loss were not established but most probably related to disruption of the normal maternal embryofetal hormonal relationship required for the maintenance of pregnancy.
3. Data from non-human primates, the most physiologically relevant animal species, suggested a small increase in pregnancy loss at around the equivalent Primodos dose when given daily for 30 days during early pregnancy.
4. Sensitivity to the embryo-lethal effect of norethisterone acetate and ethinylestradiol was species specific.
5. Genital tract abnormalities/ malformations including virilisation of female fetuses had been reported in rodents and non-human primates exposed to these hormones during the period of sexual differentiation. The developmental effects on male and female reproductive tissue reflected the known hormonal action of these compounds.
6. Genetic toxicity studies of ethinylestradiol and norethisterone acetate, alone or in combination, indicated that these hormonal agents do not directly interact with DNA, as evidenced by the negative mutagenicity results, but under some circumstances they may produce nonspecific chromosomal damage.
7. In rodents and rabbits there was evidence that norethisterone acetate and ethinylestradiol combinations could increase the frequency of skeletal variations. Such effects were generally not considered to be mechanistically linked to malformation, generally improved post-natally and were often seen in the presence of maternal or embryofetal toxicity.
8. In mice there was evidence that a combination of norethisterone acetate and ethinylestradiol given throughout organogenesis at doses that were embryo lethal was associated with an increase in thoracic malformations.
9. There was no robust evidence from studies in rats, rabbits, and non-human primates that a combination of norethisterone acetate and ethinylestradiol administered during pregnancy directly or indirectly caused developmental malformations in non-reproductive tissue.

9.3 Non-genital malformations

9.3.1 EWG Members were asked to comment on the relevance of non-genital malformations observed in mice, compared to the lack of similar findings in other species evaluated.

9.3.2 The EWG advised that malformations observed in mice may be strain dependent and without further confirmation did not necessarily reflect findings in humans. The cumulative data from studies in rats, rabbits and non-human primates did not replicate the findings from the mouse study (Schering study 3579) for an increase in thoracic malformations.

9.4 Evidence presented by Dr Vargesson

9.4.1 EWG Members were asked how the evidence presented by Dr Vargesson impacts on the above conclusions.

9.4.2 EWG Members advised that Dr Vargesson's observations were very interesting. However, because there were gaps in the data, and because the EWG had not had full access to it, the data could not be considered in detail at that time.

9.5 Vascular disruption

9.5.1 EWG Members discussed whether, on the basis of the data presented, there is sufficient evidence that EE and/or NET could disrupt a pregnancy through vascular disruption, and whether it was aware of further important data that should be considered in relation to vascular disruption.

9.5.2 The EWG Members advised that there is no convincing evidence that EE and/or NET could disrupt a pregnancy through vascular disruption at the doses used in Primodos.

9.5.3 The Group was not aware of any further important data that needed to be taken into consideration.

9.6 Epidemiological evidence

9.6.1 EWG Members discussed the strength of the epidemiological evidence for an association between use in early pregnancy of:

I. HPTs and congenital anomalies
II. OCs and congenital anomalies
III. NETA for prevention of threatened or recurrent miscarriage and congenital anomalies
IV. EE and/or NETA (for any indication) and miscarriage

9.6.2 EWG Members advised that, since all of the studies suffered from methodological problems, it was critical to ensure that the each relevant study was reviewed in an objective and unbiased manner. In order to facilitate this, a re-assessment of individual studies based on quality scores and Forest plot presentations should be conducted and brought to a future meeting.

9.7 Any other Business

9.7.1 EWG Members looked ahead to the finalisation of the review and advised that it was important to be fully transparent and recommended that final versions of all assessment reports considered by the Group should be made public together with a lay summary. EWG Members should have approval of the final documents before their release.

10. Meeting Close

10.1 The Chair advised that the Secretariat will soon be sending an email containing a Doodle Poll of potential dates for the next meeting.

Annex I - Letter from Mrs Lyon to the Group

Association for Children Damaged
by Hormone Pregnancy Tests

Dear Dr. Gebbie,

Thank you for allowing me to read out the letter of explanation and apology to the EWG at our meeting on 18th October. I am also grateful for your decision to allow me to comment on presentations delivered by the MHRA. Thank you.

I felt it was necessary to read the letter to the Group, to ensure that the they understood they were not the focus of the Debate. The concerns expressed by MP's on behalf of their constituents were specific to two members of the EWG. The main purpose of the Debate was to highlight issues with the role of the MHRA as Secretariat. The reasons for this misunderstanding were made clear in my letter and conversations I was able to have with members of the Group on the 18th October.

I was extremely dismayed by the anger and upset expressed by Mr. Evans, who I have the highest respect for and was unhappy that I could not respond to him immediately to correct the misunderstanding. I will write to Mr. Evans directly and enclose the letter read to the EWG at the meeting. I would be very unhappy if Mr. Evans resigned, as I believe he is a very valuable member of the Group.

I was further dismayed at the remarks by Ms. Yates, who appeared to take as a personal attack, the issues discussed during the Debate, instead of understanding the real concerns of MP's who were supporting their constituents. I absolutely agree that Ms. Yates should not have been identified by name, but it was essential that an example of these concerns was highlighted. However, this does not change the fact that the Association members believe that Ms. Yates does have a conflict of interest, particularly in light of the previous Report for the Association and the further report from Dr. Daniel Poulter, which is still on the MHRA website. Unfortunately, I was not allowed to engage in dialogue with Ms. Yates at the meeting, to explain these points.

The whole purpose of the debate was detailed in the Motion, which documented the issues of great concern to both the members and their MP's. These concerns were not about the other members of the EWG, but concerned the members referred to in my letter of the 18th October and the Secretariat of the EWG.

I fully appreciate the feelings of the EWG members and must again express that the purpose of the Debate was to bring forward publicly the concerns the members have about the evidence to be assessed, not about the competence of the Group.

I felt personally attacked by the remarks made by Prof. Axel Heep at the end of the meeting, regarding the" German documents" and I hope that these remarks were captured in the Minutes of the Meeting.

The response by Dr. Ord, which related to the Dr. Inman correspondence, was inaccurate and disingenuous and I would please request that these documents are available for scrutiny by the EWG.

I would like to declare that the following comments are for the attention of the MHRA Secretariat and not a criticism of your Role as Chair.

I would like to express my disappointment at the time allotted to Dr. Vargesson, who had prepared a presentation on his recent study into the effects of the components of Primodos.

I am not aware that there has been any other recent research into the actual components of Primodos and yet Dr. Vargesson was designated approx. 20 minutes to share this research with the Group. This was another indication of the EWG being denied the opportunity to assess and discuss a very important study, which was absolutely relevant to the EWG process.

I was heartened by the interest shown by the Group in Dr. Vargesson's work and their desire to see the completed study and not just a snapshot of his findings. I am aware that Dr. Vargesson will be submitting his work for publication and the EWG have requested a copy of the completed work, which should be available by the end of the year, or in the first 2 months of next year.

I anticipate that this study will be part of the decision making process.

Members who were not involved in the decision process, including me, were asked to leave the meeting to allow conclusions to be made by the decision panel.

I take for granted that the inaccuracies I highlighted in the presentations, were referenced and the evidence adjusted accordingly. One example is the number of studies identifying a negative conclusion. There were 31 positive studies and of the remaining studies, at least 8 were tainted by conflict of interest/bias. I am happy to expand on the evidence for exclusion of these studies and other information presented.

Although a study by Heinenon was discussed, it was also shown to have been disputed by Wiseman and Dodds, who are employees of Schering. Wiseman as a Scientist and Dodds Smith, a member of Schering's Law firm. However, you failed to counter this with the study by Hook, which re-visited the critique by Wiseman and Dodds and found that in fact the result increased the possible link.

There was also reference to studies by Nora and Nora, which again were not delivered in a positive manner, even though their evidence was instrumental in gaining a *high 5 figure sum* in the case against Squibb for their HPT, Gestest. You will of course be aware that Gestest had the exact components of Primodos at a very slightly higher dose and comprised of 4 tablets, taken in 2 days, yet no mention was made of this extremely important evidence.

I would like to request that this letter is placed with the copy of the letter of apology you requested, so that a complete record of the events of the 18th October will be available on the MHRA files.

Yours sincerely,

Marie Lyon (Chair ACDHPT)

Home: [redacted]
E-mail: [redacted]
Home Tel: [redacted]
Mobile: [redacted]
Web Page: [redacted]

NOT FOR PUBLICATION

COMMISSION ON HUMAN MEDICINES

HORMONAL PREGNANCY TESTS WORKING GROUP

Minutes of the meeting held on Monday 27th March 2017 at 10:00 in G1, Ground Floor, 151 Buckingham Palace Road, Victoria, SW1W 9SZ

Participants Present

Members

Dr A Gebbie (Chair)
Professor P Doyle
Professor S Evans
*1 Professor J Harper
*7 Professor Dr A Heep
*2 Professor S Hillier
*3 Professor A Macfarlane
*4 Ms S Payne
*5 Dr C Smith
*7 Professor M Threadgill
Dr D Wellesley

Invited Experts

*7 Mr N Dobrik
*7 Professor H Dolk
*6 *7 Professor F Williams
*6 *7 Dr L Yates

Observers

*7 Mrs M Lyon

*7 PD Dr E Röhrdanz

Apologies

Professor L Aarons
Mrs J Epstein
Professor K Marshall
Dr I Petersen
Mrs F Pradhan
Professor S Price
Professor S Quenby
Dr R Quinton

Professional Staff of MHRA Present

Supporting Specific Items	Item
Dr J Beynon	4.2
Mrs S Morgan	5
Dr J Nooney	4.3
Dr S Seabroke	4.1, 4.2
Dr J Woolley	8

Observers

Mr J Clements
Mr M Dykes

*1 *left at 16:36 during item 8*
*2 *left at 17:00 during item 8*
*3 *left during the lunch break (12:42-13:35)*
*4 *left at 14:32 during item 6*
*5 *left at 17:08 during item 8*
*6 *arrived at 10:17 during item 4.1*
*7 *left during the coffee break (14:38-15:02) before the members only section of the meeting*

24/7/17

Secretariat
Ms F Norris (Secretary)

MHRA Legal
Ms K Foster

1. Introduction and Announcements

1.1 The Chair reminded those present that the papers and proceedings are confidential and should not be disclosed and that all mobile phones must be switched off.

1.2 Apologies were received from:

- Mrs Joyce Epstein
- Professor Kay Marshall
- Mrs Farrah Pradhan
- Professor Shirley Price
- Dr Irene Petersen
- Dr Richard Quinton

1.3 The Chair advised that Dr Anne Connolly and Mr Ian Currie will no longer participate in the HPTWG.

1.4 The Chair reminded those present to declare any personal interests (e.g. shares, lecture fees, consultancy, travel/accommodation costs or other direct remuneration) in the following associated companies:

Successors of the companies who originally marketed HPTs:

- Alinter Group
- Bayer plc
- GlaxoSmithKline UK
- Marshall's Pharmaceuticals Ltd
- Merck, Sharpe and Dohme Ltd
- Pfizer
- Piramal Healthcare Ltd
- Sanofi

The companies who originally marketed HPTs:

- Roussel Laboratories
- Parke Davis
- Wallace Manufacturing Chemists Ltd
- Schering
- Organon Laboratories
- Nicholas Laboratories Ltd
- Duncan Flockhart and Company Ltd.

The Chair reminded participants to declare the nature of any involvement they may have had with HPTs (e.g. reviews of these products, public commentary on their safety).

The Chair directed participants to **Tabled Paper I** – an updated list of the HPTWG declared interests.

The Chair advised of the following:

Professor Harper:
"I attended a conference in Taiwan in 2009 that was hosted by Schering Plough Taiwan Ltd Organon Women's Health & Fertility. I was only there for one night. I gave a talk and came straight back. They paid my travel but I did not get any income from it. The conference was about fertility and had nothing to do with HPTs.
Also I do not think this is a conflict but I think we should also acknowledge that I run a public engagement group to discuss women's health issues – www.globalwomenconnected.com. I write articles that are open to the public but I have never written anything about HPT".

The Chair advised participants that there was no change to the status of Professor Harper's participation as a Member in light of the new information declared.

2. Minutes from the meeting held on Tuesday 18th October 2016

2.1 The Group discussed the minutes of the meeting held on Tuesday 18th October 2016. The minutes were approved as an accurate record of proceedings, subject to minor amendments.

3. Matters Arising

3.1 Feedback on the conference on HPTs at Cambridge University on 31st January 2017

3.1.1 The Group was informed that presentations at the conference focussed on the historical and regulatory context from the period when HPTs were marketed in the UK and a comparison of regulatory actions taken in different countries. The programme included a screening of the London Programme ("Primodos: The Secret Drug Scandal", 1978); a talk by Mrs Lyon based on documents obtained from the British National Archive and the Landesarchiv Berlin; a discussion of the UK drug regulation before and after thalidomide (John Abrahams, Kings College) and a talk about the difficulty of the decision-making process with evidential uncertainty (Tim Lewens, Cambridge University). Researchers from France, Finland, Norway and Sweden had been searching the archives of their national regulatory authorities and spoke about their preliminary findings. Dr Vargesson concluded the meeting with a presentation of the work that he previously presented to the EWG.

3.2 Feedback on the screening of the Sky News documentary

3.2.1 The Group noted that the Sky News documentary, screened in the House of Commons on 21st March, raised many of the same issues discussed at the Cambridge conference and relied heavily on the information retrieved from the British National Archives, the documents from the Landesarchiv Berlin

and files provided by Mr [redacted]. Key claims included: i) a 5:1 relative risk of anomalies among children born to women who had used an HPT; ii) the destruction of study participation information; iii) an unhealthily close relationship between regulator and industry; iv) negligence by the company (Schering); and v) use of a double dose of Primodos as an abortifacient in Korea.

3.2.2 The Group was reminded that it had already received all documents retrieved from the National Archives and the Landesarchiv Berlin and that it would shortly be sent the files submitted by Mr [redacted] for consideration at the next meeting. Mr Dobrik said he had not seen the documentary but that issues raised would need to be taken into consideration when making recommendations for the future.

3.2.3 The Group were reminded that they should refer any queries from the media (should they be approached) to the MHRA Press Office.

4. Review of the epidemiological evidence

4.1 Re-analysis of the epidemiological evidence for a possible association between HPT use and congenital anomalies (MHRA Paper 1)

4.1.1 The Group was presented with a re-analysis of the epidemiological evidence for a possible association between HPT use and congenital anomalies. This used a formal quality scoring system, devised by the assessor and agreed with Professor Doyle, to indicate the quality of the study; presented the results as forest plots; and presented studies of limb reduction defects separately from studies of all limb defects, in line with recommendations made by the Group at the previous meeting.

4.1.2 The Group considered the reanalysis to be a clear presentation of the evidence and the best that could be done with the data.

4.1.3 Reasons for the quality scores attributed to some of the studies were discussed. The Group suggested that women who proactively sought to know their pregnancy status and who were given a HPT may have a different the baseline risk for birth defects (perhaps because of previous complications of pregnancy) than women who were not given an HPT, which might bias the results. In this context, by comparing the women who used an HPT with women who used a different type of pregnancy test, the study by Torfs had the most appropriate control group - an aspect which was a limitation in all other studies. However, this advantage was offset by its small sample size, lack of control for confounding and the different time periods for cases and controls, making it difficult to draw conclusions. The Group considered that the same sorts of biases, including ascertainment of exposure, also occur in epidemiology studies today, but are generally reported better. Further, it was important to recognise that biases could not only inflate results but also obscure true associations and this needed to be made explicit in the paper.

4.1.4 The Group discussed the criteria used by the assessor to conclude that a small risk of certain anomalies "cannot be excluded". It was explained that this wording had been used when point estimates for studies relating to a particular anomaly were consistent with a small increase in risk despite being the results being insignificant and the study confounded. The Group agreed with this definition and considered it an important point that should be made clear in the report.

4.1.5 The Group questioned the appropriateness of including the study by Tummler, since this was based on spontaneous reporting data. It was explained that this had been included for completeness and the Group agreed that the paper made it clear that the study was considered to be "of very poor quality".

4.1.6 The Group discussed whether the data were amenable to a meta-analysis and agreed that because the studies were so different such an analysis would not be informative but that this point should be made clear in the report. Furthermore the report should explicitly state why a numerical scale was not considered appropriate and why studies were not weighted. The term 'robust' should be defined and consistent with accepted definitions.

4.1.7 Mrs Lyon questioned why the Heinonen study, which appeared to be very large, was scored as small-moderate in size; it was explained that this was because the studies were scored on the number of women who were exposed to HPTs (rather than total number of women included), which was relatively small in the Heinonen study.

4.1.8 There was some discussion over the transcript of a conversation between Dr Inman and Schering which refers to a 5:1 relative risk of anomalies in women who used HPTs and upcoming publication of the findings. The Group considered that there was a lack of clarity over what outcome the relative risk referred to and it was noted that a 5 fold risk was not reported in the interim results of the CSM study that were published 5 months later. Mrs Lyon expressed the view that this related to the risk of birth defects in children born to women who used HPTs. It was suggested that MHRA tries to contact the study author, Dr Gillian Greenberg for clarification.

4.1.9 Refer to section 5 for conclusions and recommendations of the members.

4.2 Further analysis of spontaneous reports with Hormonal Pregnancy Tests (MHRA Paper 2)

4.2.1 The Group noted **Tabled Paper II**.

4.2.2 The Group heard that additional analysis of the spontaneous reporting data had been carried out by MHRA as requested. The updated analyses included:

i. comparing the proportions of each of the different major anomalies in the HPT-exposed data with the proportions present in the EUROCAT dataset and the British and Irish Network of Congenital Anomaly

Researchers (BINOCAR) datasets, to determine if there were any increased proportions in the HPT-exposed group that could indicate a drug-related effect

ii. comparing the proportions of each of the different major anomalies present in the HPT-exposed data with the proportions reported for all other drugs in the MHRA Yellow Card database collected since its inception, to determine if there were any increased proportions in the HPT-exposed group that could indicate a signal of a drug-related effect.

4.2.3 The Group commented that: 1) a highly conservative approach had been taken when excluding genetic diagnoses, such that only cases known to be due to chromosomal causes were excluded (all other cases were included); 2) the BINOCAR data form a subset of the EUROCAT dataset; 3) while there have been some exceptions (e.g. thalidomide), the nature of spontaneous data meant it was not possible to have strong evidence of a drug-related association with any congenital anomaly; and 4) while limb reduction defects were consistently higher as a proportion of all anomalies, this may be a reporting bias rather than a true association.

4.2.4 The Group recognised that the most important difference between the various datasets was the way in which the data had been reported/collected such that the reports from the Association for Children Damaged by Hormonal Pregnancy Tests were different in nature, quality and duration of follow-up to those in the EUROCAT/BINOCAR or MHRA Yellow Card datasets. Any analyses involving the data from the Association therefore needed to be interpreted carefully because when the Association's dataset was excluded there was no clear evidence of risk of congenital anomalies with HPTs.

4.2.5 Mr Dobrik asked about the proportion of genetic versus non-genetic cases and was informed that this was constantly changing, as the ability to detect genetic cases increases. Mr Dobrik was informed that it was not possible to include cases of learning difficulty in the analysis because the terminology relating to learning difficulties has changed over time, there is no ICD10 code for mental retardation alone so cases of developmental delay are only included in EUROCAT/BINOCAR if there is also a structural anomaly, and spontaneous data are not good for capturing such reactions with a long time to detection from the original exposure.

4.2.6 Overall, the Group was in agreement with the conclusions of the paper and considered that no further analyses were necessary or possible.

4.2.7 Mrs Lyon considered that the correct approach had been taken to the exclusion of cases with a possible genetic diagnosis and had no further comments.

4.2.8 Refer to section 5 for conclusions and recommendations of the members.

4.3 Possible effect of NETA/EE on the developing fetus: evidence from pharmacological data (MHRA Paper 3)

4.3.1 This paper examined the pharmacological evidence to see if the components of Primodos (ethinylestradiol, EE and norethisterone acetate, NETA), when used to diagnose pregnancy, could have had a direct effect on fetal development. NETA is converted to norethisterone (NET) immediately after oral administration, so the paper refers to NET and its metabolites. The assumption was made that, in order for the EE and NET to have an effect on the developing fetus, there would have to be functional estrogen receptor and progesterone receptor expression in the fetus and that sufficient EE and NET would have to reach and activate these receptors.

4.3.2 The Group was informed that the paper had been updated in line with their previous comments and that information relating to the effects of EE/NETA in animal studies was not re-presented because it had been considered separately. Full reviews of the data were provided as annexes to the paper.

4.3.3 The Group noted the updates. The Group discussed the elimination of drugs from the fetus and the fact that any possible retention by the fetus would apply to all drugs. A number of factors that remain unknown were highlighted including: whether EE and NET were pharmacologically so similar to maternal estrogen and progesterone that they were removed via transfer back to the mother; whether any fetal receptors that might be present were functional; whether there was a gender specific difference.

4.3.4 The Group discussed the fact that fetuses with anomalies were usually spontaneously aborted and questioned whether there was evidence that a) by preventing a failing pregnancy HPTs were preventing women from spontaneously aborting and b) any spontaneously aborted fetuses had anomalies. The Group was reminded that a previous paper had considered the evidence for a possible association between HPTs and congenital defects in women who had taken hormones to prevent a spontaneous abortion [meeting 4] and that some, but not all, of the studies had included examination of the aborted fetuses. Overall the evidence was not strong but there was no evidence that hormones were either preventing or causing miscarriage, nor was there any obvious evidence of teratogenicity.

4.3.5 Mrs Lyon referred to a very small study in which some bleeding was observed within two days of taking HPTs and questioned if could be related to thrombosis. It was agreed that this was likely to have been a withdrawal bleed caused by the fall in hormone levels.

4.3.6 Overall the Group considered that there remained substantial uncertainty around the quantitative aspects of exposure and that, whilst the amounts of NET and EE provided through HPTs were likely to be sufficient to reach the fetus their levels would be lower than those of maternal hormones already present in pregnancy. Because there was so much uncertainty it was important that the worst case scenario had been considered.

4.3.7 The Group commented that this paper represented a very reasonable interpretation based on the evidence that was available.

4.3.8 Refer to section 5 for conclusions and recommendation of the members.

5. Valproate – risks in pregnancy (MHRA presentation)

5.1 In response to an earlier request from the Group, the MHRA outlined the key UK regulatory milestones in relation to the evaluation of valproate in pregnancy and risks of birth defects and neurodevelopmental disorders, described the work taking place to implement risk minimisation measures, and discussed the lessons that had been learnt.

5.2 Lessons learnt include that: i) engagement with patients/patient groups was important to inform regulatory decision-making; ii) close monitoring of the impact of action was important; iii) communications may need to be repeated through multiple channels; iv) health professionals receive multiple messages from different bodies in the health system which can give rise to alert fatigue; and v) being aware of an issue did not necessarily lead to a change in behaviour and 'forcing functions' or restrictive action may be needed.

5.3 The Group discussed the reason for the length of time it had taken for evidence of the magnitude and nature of developmental disorders to become apparent and that this highlighted the need for better systematic collection of data on outcomes of the use of medicines during pregnancy. Other discussion points related to the need for better ways to disseminate information to healthcare professionals (HCPs) and to women, better ways to audit HCPs, greater acceptance that pharmacovigilance and signal analysis is a public responsibility. However, the key question was how the safety of medicines given to women to childbearing age can be better monitored.

5.4 The Group agreed that these issues should be a high priority for discussion at the next meeting.

6. Any Other Business

6.1 Professor Dolk suggested that the report of the Group might include a guide to hierarchy of evidence and suggested that the Group looks at different systems for the terminology relating to classification of evidence.

6.2 Mr Dobrik asked that he and Dr Yates (both 'invited experts') are allowed to remain to participate in the formulation of the Members' conclusions and recommendations in relation to the lessons learnt remit at the next meeting. Mr Dobrik was advised by the MHRA lawyer that there would need to be a very strong reason for changing participation rules and limits from those agreed prior to the commencement of the Group. Dr Yates considered that having involvement in the Group's discussions on this aspect prior to the formulation of the conclusions and recommendations was acceptable to her and that she did not also need to be included in the Members' formulation of

the conclusions and recommendations. Dr Gebbie advised Mr Dobrik that she would consider and let him know of her decision in due course.

6.3 The agenda of the next meeting was discussed and Professor Hillier suggested that a summary outline of the key points in the history of HPTs and congenital anomalies could be helpful.

6.4 When asked, Mrs Lyon had no other comments to add.

7. Date of Next Meeting

7.1 The Group was reminded that the next meeting is on 24th April. The agenda will include:

- a presentation of the available information from the National Archives, the Landesarchiv Berlin and from Mr [redacted]
- a presentation of the key points from the HPT conference held in Cambridge on 31st January 2017
- a paper on lessons learnt with respect to identifying, assessing and communicating drug safety concerns in pregnancy.

8. Meeting conclusions and recommendations - Advice sought (MHRA paper 4)

In line with the participation definitions provided to the Group at the beginning of the review, Invited Experts and Observers are not permitted to contribute to conclusions and recommendations and so left the meeting at this point.

8.1 Re-analysis of the epidemiological evidence for a possible association between HPT use and congenital anomalies (MHRA Paper 1)

8.1.1 The Members considered that the re-analysis of the epidemiological evidence for a possible association between HPT use and congenital anomalies demonstrated clearly that the quality of the evidence was generally too poor to enable any firm conclusions to be drawn and that the limitations of the studies meant that even if an association were to be found it would not necessarily be indicative of a causal association. Nevertheless, the available data suggested that use of HPTs was not associated with an overall increase in the risk of congenital anomalies. Furthermore, the available data did not suggest a strong association with any single anomaly, nor was there evidence of an association with any particular combination or pattern of defects.

8.1.2 With respect to the specific anomalies, the Members endorsed the conclusions of the re-analysis as follows:

1. A small increased risk of congenital heart defects, limb reduction defects and oesophageal atresia associated with HPTs could not be excluded.

2. There was no robust evidence of an association between HPTs and nervous system defects (excluding neural tube defects), orofacial clefts or VACTERL.
3. The results of the studies did not suggest an association between HPTs and neural tube defects, digestive system and abdominal wall defects (other than oesophageal atresia), skeletal defects (other than limb reduction defects) and overall congenital anomalies.
4. There was insufficient data for urinary system and genital defects to draw any conclusions.

8.1.3 The Members considered that the distinctions between some of the conclusions relating to the level of evidence available with respect to the different anomalies should be clarified and the language made more lay friendly in the final report.

8.2 Further analysis of spontaneous reports with Hormonal Pregnancy Tests (MHRA Paper 2)

8.2.1 The Members endorsed the conclusions of the further analysis of spontaneous reports with HPTs as follows:

1. The HPT-exposed cases compiled for this assessment were small in number (n=235) and many were limited by absent medical confirmation or insufficient case details.
2. Eighteen per cent of the cases involved possible multiple congenital anomalies but no clear pattern was seen within them to suggest an identifiable syndrome.
3. Comparison of the HPT-exposed dataset with the EUROCAT dataset showed a higher proportion (≥2 fold difference) of 18 anomalies. The 6 anomalies with the greatest difference in proportion compared with the EUROCAT dataset were: anophthalmos; limb reduction defects; anophthalmos/microphthalmos; situs inversus; congenital glaucoma and tricuspid atresia and stenosis.
4. Comparison of the HPT-exposed dataset with the BINOCAR dataset showed a higher proportion (≥2 fold difference) of 17 anomalies. The 6 anomalies with the greatest difference in proportion compared with the BINOCAR dataset were: anophthalmos; limb reduction defects; transposition of great vessels; situs inversus; congenital glaucoma and anophthalmos/microphthalmos.
5. When comparing the HPT-exposed dataset from the UK with the MHRA Yellow Card database for all drugs, a higher proportion of cases specifically described 'limb reduction defects' in the HPT-exposed dataset (7.3% vs 2%). The MHRA spontaneous cases were noted to be much less detailed than the HPT-exposed dataset, with many non-specifically coded cases, and any differences must therefore be interpreted with caution.
6. Overall, in light of the limitations of the data, the further analyses did

not provide strong evidence of an identifiable congenital anomaly, or pattern of anomalies, associated with HPT exposure in women.

8.2.2 For the final report, the Members considered that the observations would need to be re-worded to provide greater context and make them more suited to a lay audience.

8.3 Possible effect of NETA/EE on the developing fetus: evidence from pharmacological data (MHRA Paper 3)

8.3.1 The Members concluded that there was no clear evidence that taking Primodos during the first trimester of pregnancy could cause congenital anomalies via a direct pharmacological action; however, because the evidence was limited and many factors remained unclear, such an effect could not be definitively excluded.

8.3.2 The Members endorsed the observations made with respect to a possible effect of NETA/EE on the developing fetus, based on pharmacological data as follows:

- Based on animal data, it was likely that EE and NETA crossed the placenta in human pregnancy during development of the fetus
- The concentration of NET from a single Primodos tablet that crossed the placenta may have been high enough to bind to progesterone receptors, depending on the extent to which NET was protein-bound in the fetus and how much competing endogenous fetal progesterone was present
- The concentration of EE from a single Primodos tablet that crossed the placenta may have been high enough to bind to estrogen receptors, if there was no, or minimal, protein-binding in the fetus, and depending on how much competing endogenous fetal hormone may have been present
- Limited data from animal studies suggested that estrogen and progestogen receptor expression in the fetus occurred relatively late in development and around the end of the period of organogenesis in both reproductive and non-reproductive tissue; expression in the latter may be transient.

8.3.3 For the final report the Members considered that the observations on the data should provide greater context and the language made more suitable for a lay audience.

9. <u>Any Other Business/Meeting Close</u>

9.1 The Members had a general discussion about the final report of the Group and emphasised the need to ensure it was suited to its target audience, that technical terms were explained clearly, the data presented in context and their limitations clearly explained. Members also thought it important to consider carefully how best to express uncertainty and level of risk.

NOT FOR PUBLICATION

COMMISSION ON HUMAN MEDICINES

HORMONAL PREGNANCY TESTS WORKING GROUP

Minutes of the meeting held on Monday 24th April 2017 at 10:00 in Church House Westminster, Deans Yard, Westminster, London SW1P 3NZ

Participants Present

Members

Dr A Gebbie (Chair)
Professor P Doyle
*1 Mrs J Epstein
Professor S Evans
*2 Professor J Harper
Professor S Hillier
Professor A Macfarlane
*3 Ms S Payne
*4 Mrs F Pradhan
Professor S Price
Professor S Quenby
Dr C Smith
Professor M Threadgill
Dr D Wellesley

Invited Experts

Professor L Aarons
Mr N Dobrik
Professor H Dolk
Professor K Marshall
Dr I Petersen
Professor F Williams
*5 Dr L Yates

Observers

Mrs M Lyon
PD Dr E Röhrdanz
*6

Visiting Experts

Dr J Olszynko-Gryn

Professional Staff of MHRA Present

Supporting Specific Items **Item**

Dr J Woolley

Observers

Mr J Clements
Mr M Dykes
Mrs S Morgan
Dr J Nooney
Dr J Raine

*1 *left at 16:30 during item 10*
*2 *left at 16:37 during item 10*
*3 *left at 13:20 during the lunch break (13:00-13:44)*
*4 *left at 16:45 during item 10*
*5 *arrived at 10:17 during item 3*
*6 *left at 14:35 during item 6.1*
*7 *left during the afternoon break (14:59-15:25) before item 9*

24/7/2017

Apologies
Professor Dr A Heep
Dr R Quinton

Secretariat
Ms F Norris (Secretary)

MHRA Legal
Ms K Foster

1. Introduction and Announcements

1.1 The Chair reminded those present that the papers and proceedings are confidential and should not be disclosed and that all mobile phones must be switched off.

1.2 Apologies were received from:

- **Professor Joyce Harper**
- **Dr Richard Quinton**

1.3 The Chair reminded those present to declare any personal interests (e.g. shares, lecture fees, consultancy, travel/accommodation costs or other direct remuneration) in the following associated companies:

Successors of the companies who originally marketed HPTs:

- Alinter Group
- Bayer plc
- GlaxoSmithKline UK
- Marshall's Pharmaceuticals Ltd
- Merck, Sharpe and Dohme Ltd
- Pfizer
- Piramal Healthcare Ltd
- Sanofi

The companies who originally marketed HPTs:

- Roussel Laboratories
- Parke Davis
- Wallace Manufacturing Chemists Ltd
- Schering
- Organon Laboratories
- Nicholas Laboratories Ltd
- Duncan Flockhart and Company Ltd.

The Chair reminded participants to declare the nature of any involvement they may have had with HPTs (e.g. reviews of these products, public commentary on their safety).

2. Minutes from meeting held on Monday 27th March 2017

2.1 The Group discussed the minutes of the meeting held on Monday 27th March 2017. The minutes were approved as an accurate record of proceedings, subject to minor amendments.

2.2 When asked, Mrs Lyon had no comments on the minutes.

3. Matters Arising

3.1 The Group heard that a sample letter to Genetics Departments had been drafted by Dr Wellesley, Professor Dolk, Professor Doyle and Dr Yates that could be used in the event of a recommendation to offer members of the Association for Children Damaged by HPTs full diagnostic assessment.

3.2 The Chair referred the Group to a set of papers published recently in JAMA (provided by Dr Petersen) on exposure to antidepressants in pregnancy and possible association with a range of adverse pregnancy and child outcomes. These studies illustrated the limitations associated with evaluating drug safety in pregnancy, but also demonstrated the use of innovative statistical techniques to overcome some of the issues.

3.3 The Group heard that the MHRA had asked Dr Haskey, the statistician who had carried out the analyses and tests for the CSM's "Maternal Drug Histories" study, about the claim that Dr Inman had said that drug monitoring in pregnancy over the last five years had shown that "*among those who had had a hormonal pregnancy test, there is a relative risk of 5:1 in having a deformed child*." Dr Haskey did not recall a figure of 5 for the relative risk observed in the CSM's study. MHRA then contacted Dr Greenberg, the main author of the study but she did not respond.

3.4 In response to Mr Dobrik's request that, as an 'invited expert', he should be allowed to remain to participate in the formulation of the Members' conclusions and recommendations in relation to the lessons learnt remit, the Chair advised there to be no strong reason to make any amendments to the participation rules at this late stage in the proceedings.

3.5 Dr Raine thanked the Group for their rigorous examination of the evidence relating to the EWG terms of reference and emphasised particularly the importance of considering the future with respect to how the identification, assessment, management and communication of drug safety issues in pregnancy can be further strengthened. Dr Raine informed the Group that a report of their work will be considered by the Commission on Human Medicines (CHM) and that CHM will advise the Licensing Authority (health ministers) of the EWG's conclusions and recommendations in the Autumn. A draft of the report will be shared with the Group prior to its consideration by CHM.

3.6 The Chair thanked the MHRA secretariat for their support and thorough assessments of the evidence.

4. Feedback from the Cambridge Conference on "The Contested History of Hormone Pregnancy Tests"

4.1 The Group heard a presentation from Dr Jesse Olszynko-Gryn (Oxford University) which covered the alternative pregnancy tests that were available when HPTs were on the market, the regulatory and legal context within Britain at that time, and the actions taken with HPTs in other countries. Dr Olszynko-Gryn stated that review of this issue by academic historians was ongoing and concluded by questioning how we can best learn from the past

to inform regulatory processes in the future.

4.2 The Group thanked Dr Olszynko-Gryn for his presentation. Referring to the different actions taken with respect to HPTs within the different countries, the Group agreed that as well as scientific considerations, non-scientific factors such as the legal and cultural context and possible public health consequences contribute to regulatory decision-making. Regarding the apparent concern of the Committee on Safety of Drugs (CSD) that taking action against HPTs could have adverse consequences for combined oral contraceptives (COCs, the 'Pill'), Dr Olszynko-Gryn was asked whether there had been any Pill scares in the countries that had taken action with HPTs earlier than the UK. Dr Olszynko-Gryn said that he thought the market for COCs was smaller in the Scandinavian countries than in the UK at the time but that this was an important point to consider.

4.3 The Group discussed the difficulties associated with evaluating historical data noting, in particular: the lack of accurate data on HPT exposure; and the inability to compare the risks associated with the injectable versions of HPTs (which contained natural progesterone and estradiol benzoate) with the oral versions (which contained synthetic hormones) due to a lack of information on the many different hormonal products that were available at the time.

4.4 In response to Dr Olszynko-Gryn's question about the nature of the ideal control group for the epidemiological studies on HPTs, the Group stated that ideally the baseline risk to the fetus in a woman exposed to an HPT would have to be the same as the baseline risk to the fetus of a woman who had not been exposed, and that designing such a study remained one of the key limitations with the available epidemiological evidence. The Group considered that the study by Torfs had a more appropriate control group than most of the other studies they had reviewed and which had compared women exposed to HPTs with women who had no test for pregnancy (and were therefore likely to have different risk factors).

4.5 When asked for his view on why it had taken so long for the adverse effects of valproate to be recognised, Dr Olszynko-Gryn commented that he had no informed view on valproate but that generally it was more difficult to identify developmental adverse effects in association with use of a medicine during pregnancy than it was physical anomalies.

5. Consideration of additional information submissions

5.1 Updated schedule of documents (MHRA Paper 1)

5.1.1 The Group heard that the schedule of documents (considered twice previously) had been updated to reflect the documents received from Mr [redacted] in November 2016 and that the bulk of these related to action taken with HPTs in India. Other documents related largely to: correspondences; press clippings; documents from Schering Chemical Ltd, UK; CSD/CSM documents; and scanned images of Primodos labelling.

5.1.2 The updated schedule also included the foreign language documents from the Landesarchiv Berlin that had been provided by Mrs Lyon and for which MHRA had arranged professional translation. The translated documents had been sent to the Group in February 2017.

5.1.3 Most of the translated documents appeared to originate from Schering AG in Germany and included a wide variety of correspondences, minutes of meetings, briefings, sales data and documents detailing regulatory action taken in Germany and globally with respect to Primodos, Duogynon and Cumorit.

5.2 Documents from the Landesarchiv Berlin (presentation by Mrs Lyon)

5.2.1 Mrs Lyon's presentation included: the results from a selection of Schering reproductive and developmental studies in rats and rabbits, which provided the human equivalent doses (HEDs) for ethinylestradiol and norethisterone; a chronology of events leading up to the action taken by CSD/CSM; and the importance of the pre-clinical work by Dr Vargesson in chick embryos and zebrafish (previously presented to the Group).

5.2.2 The Chair thanked Mrs Lyon for the interesting overview. The Group questioned the information presented on the alleged use of HPTs as abortifacients, in light of current evidence that emergency contraception works by delaying ovulation rather than causing abortion (accepting that emergency contraception contains a different hormone to Primodos). Further, the Group noted that a recent large study had found that progesterone did not have any effect on miscarriage rates, even when given at high doses[1].

5.2.3 The Group noted the findings of the Schering animal studies that had been highlighted by Mrs Lyon and commented that these and all other known Schering studies had been reviewed and presented to the Group in detail. The reminder of the HEDs was useful nonetheless. The Group also noted: the absence of toxicokinetic (exposure) data for most studies considered; the reporting of a small number of fetal changes in the studies; and the evaluation of small numbers of animals. The Group commented that the criteria for establishing a teratogenic effect typically includes demonstrating a dose effect in sufficient numbers of animals and in more than one species. Taken overall the Group remarked that the findings in the animal studies from different sources had been remarkably consistent in showing an impact on resorption of the embryo at high concentrations of ethinylestradiol and norethisterone acetate but had provided little evidence for an increase in malformations, even at these high hormone concentrations.

5.2.4 The Group noted that questions had been raised about the actions of the regulators and the company when HPTs had been on the market and agreed

[1] Coomarasamy A, Williams H, Truchanowicz E et al. (2015). A randomized trial of progesterone in women with recurrent miscarriages. NEJM;373:2141-48.

that while it was important for transparency for the Group to have been provided with all historical documents available to the MHRA, it was not within their remit, and nor was it an appropriate forum, to make judgements on the past actions of individuals.

5.3 Updated chronology (MHRA paper 2)

5.3.1 The Group considered a paper on the chronology of events (based on all the documents available to the MHRA) that had been updated to include all events considered of relevance from the documents submitted by Mr [redacted] and from translations of the foreign language documents from the Landesarchiv Berlin. The Group noted that, as requested, a simplified timeline had been added as Annex 1 to the paper that included the most significant HPT-related milestones together with key UK developments in pregnancy testing and major legal and regulatory initiatives. A detailed updated summary of the events that took place in the UK from the perspectives of the company, the regulator, academic researchers, the legal profession, patients and the media was provided at Annex 2.

5.3.2 When the Group was asked if it had noted any inaccuracies or omissions to the timelines, it requested that the "5:1 risk" remark (attributed to Dr Inman) be referenced to the translated Landesarchiv Berlin documents. The Group commented that there was a considerable degree of uncertainty over this quote due to its having been made in English, recorded in German and translated back to English. The Group speculated whether the 5:1 risk cited referred to the proportional reporting ratios of ADRs associated with HPTs (based on Yellow Card reports) reported initially to the CSD, rather than to the findings of the CSM's Maternal Drugs Histories study.

5.3.3 When asked, neither Mrs Lyon nor Mr Dobrik had any other comments to add.

6. Lessons learnt and proposals for the future

6.1 Lessons learnt with respect to identifying, assessing and communicating drug safety concerns in pregnancy (MHRA Paper 3)

6.1.1 This paper looked back at the processes and tools that were available to the regulators when HPTs were on the UK market; assessed the regulatory changes that had been made since that time; described the measures in place in the current regulatory system to identify and minimise risks when medicines are taken during pregnancy; and reviewed whether any areas could be further strengthened to support the safe use of medicines in pregnancy.

6.1.2 The Group heard that when HPTs were on the UK market the socio-medical, legal and regulatory environment was very different to that today, and that many important developments in these areas had since taken place. Such developments included the extent to which patients are involved in decision-making about their treatment, the policy around medical record retention, and

systems for monitoring, and acting on, drug safety issues (pharmacovigilance). In particular, the medicines legislation relating to pharmacovigilance had undergone recent significant revision and strengthening with the introduction of Directive 2010/84 (implemented in July 2012). The Group heard that Directive 2010/84 had been drafted largely in response to limitations that had been identified within the previous legislation regarding the effective management of drug safety issues within a European environment. The new legislation sought to: 1) improve regulatory oversight of companies' pharmacovigilance systems; 2) increase proactive safety monitoring, including risk management; 3) increase transparency and give patients more of a voice; 4) accelerate EU decision-making on drug safety issues; and 5) improve co-ordination of communication.

6.1.3 The Group noted that medicines legislation was now underpinned by a range of international and EU guidance which ensured that appropriate studies were conducted prior to marketing authorisation for new drug substances intended for use in the general population, and their results analysed and interpreted consistently.

6.1.4 The Group also noted that the key principles of signal evaluation i.e. gathering additional data, seeking expert advice and taking risk proportionate action, had not changed fundamentally since HPTs were on the market but were now supported by more robust tools and legislation.

6.1.5 Regarding medicines used in pregnancy the Group noted that several pregnancy registers and congenital anomaly databases have been established, but that there was scope for further strengthening the tools currently available to detect and evaluate potential harm with medicines used in pregnancy.

6.1.6 The Group heard that MHRA was taking steps to improve how it communicated risk to healthcare professionals and patients. This includes working with other organisations within the health and social care sector across the UK to improve the impact of safety messaging. MHRA was also looking to improve how it monitors the effectiveness of action taken to minimise important risks. The Group noted that a European Good Vigilance Practice guideline on ‘Pregnancy and Breastfeeding’ is to be prepared.

6.1.7 The Group had a general discussion around the ways in which the regulatory framework had been strengthened substantially since HPTs were available in the UK and re-iterated the importance of communicating risk effectively and monitoring the effectiveness of action taken to minimise risk.

6.1.8 It was questioned whether, if the concerns about HPTs were raised in today’s regulatory environment, a more precautionary approach to the continued marketing of HPTs would be taken than previously. However, the Group considered that, for a number of reasons, this was not possible to answer.

6.2 Proposal for a pregnancy pharmacovigilance system (presented by Professor Dolk)

6.2.1 Professor Dolk, Professor Doyle, Dr Wellesley and Dr Yates provided an outline of their views on:

- the limitations of the current mechanisms for detecting and evaluating potential risks with medicines used in pregnancy
- the characteristics required for an effective pregnancy pharmacovigilance system
- the data sources currently available in the UK and;
- the importance of establishing linkages between existing data sources throughout the UK.

6.2.2 The Group heard that ideally, any proposal for an improved system would require: systematic notification of pregnancy outcomes for novel medicines; resources for multiple research/surveillance centres; and the possibility of international collaboration. Options for funding could include contributions from manufacturers of relevant pharmaceutical products as well as public/research council funding.

6.2.3 The Group agreed that there was a need for strengthened surveillance of the safety of medicines used in pregnancy within the UK and that realistically, it was good to build on what already existed. Any model should aim to collect data on miscarriage as well as anomalies, and on non-prescription as well as prescription-only medicines. The Group commented there would need to be more consideration of how to prioritise research projects, focussing on the use of medicines necessary to treat chronic conditions during pregnancy. The Group commented that animal data contributed to the screening out of drugs from further development and questioned whether i) animal and in vitro data could be used in computer modelling to generate safety signals and ii) whether molecular structure alerts could be used to prioritise drugs for study.

6.2.4 The Group acknowledged that the Scandinavian countries had the best data collection and linkage, resulting in a good surveillance model and suggested that one reason for this might be due to different cultural sensitivities over data privacy. The Group recognised that there would need to be government support for any proposal.

6.2.5 Mr Dobrik commented that it would be helpful to include a non-scientist to support any recommendations to improve data collection and monitoring in the future. This would ensure that any such proposals were made meaningful to a lay audience.

7. <u>Any other Business</u>

7.1 Before the invited experts and observers were asked to leave the room, Mrs Lyon confirmed she had no further comments to make. She also thanked the Group for their work on this review.

8. Announcements

8.1 The Chair advised the Group that next portion of the meeting would comprise of the discussion of the conclusions and recommendations. As per the participation definitions, the invited experts and observers were asked to leave the meeting at this point.

9. Meeting Conclusions

In line with the participation definitions provided to the Group at the beginning of the review, Invited Experts and Observers are not permitted to contribute to conclusions and recommendations and so left the meeting at this point.

9.1 Conclusions of the Members on the scientific evidence (MHRA paper 4 / table paper 1)

9.1.1 The Members considered Tabled Paper 1, which set out the conclusions on the scientific evidence that had been reached at previous meetings. The Members discussed in detail each of the topic areas to confirm if they remained content with their previous conclusions in the light of the totality of the evidence.

9.1.2 With respect to the **pharmacological considerations**, the Members endorsed their previous conclusions. Members commented that the conclusions in the final report should explain the use of the abbreviations NET vs NETA and place more emphasis on the presence of endogenous hormones during pregnancy (including high concentrations of progesterone).

9.1.3 With respect to the review of **vascular disruption**, the Members endorsed their previous conclusions and had no further comments.

9.1.4 Regarding the review of **animal data**, the Members endorsed their previous conclusions and suggested that when presented in the final report these should clearly refer to the route of administration, dosage, systemic exposure levels and species' sensitivities as appropriate. Members also suggested that it should be made clear that the term "developmental malformations" does not refer to an effect on the development of cognitive/mental function, and the recognised risk of virilisation should be the first conclusion. The Members suggested the report should include a glossary that includes the definitions for congenital anomalies, developmental disruption and malformations specifically.

9.1.5 The Members' previous conclusions with respect to the **spontaneous data** were endorsed. The Members commented that the report would benefit from:

- including estimates of the numbers of women exposed to HPTs to put the ADR data into context

- clarifying the number and source of the different ADR reports
- adding a caveat about the nature of the cases that were reported many years after they occurred and in response to an external stimulus
- clarifying that there were no controls or unexposed cases
- avoiding duplication of anomalies due to the overlap in coding of some conditions (i.e. removing reference to 'anophthalmus' as a separate event from 'anophthalmus/micropthalmus)
- referring to the comparisons between MHRA ADR data and the BINOCAR/EUROCAT databases as 'proportional reporting analysis' and providing the events for which there was a lower (as well as a higher) proportion in the MHRA ADR data for completeness, and
- emphasise that, unlike thalidomide and phocomelia reports, no single anomaly stands out as having been reported disproportionately.

9.1.6 The Members endorsed their previous conclusions of the review of **epidemiological data** and suggested that the report should make it clearer that the evidence was from the published literature; that it was a 're-examination' rather than a 're-analysis'; that the data were generally poor and showed no strong associations with any single anomaly, or any pattern of anomalies.

9.1.7 The Members remarked that investigating possible associations between medicines taken in pregnancy and developmental disorders in the child was very difficult but that this was not captured in any of the scientific review papers. The Members suggested this could be considered further in the Group's recommendations for the future.

9.2 Overall conclusions of the Members on the evidence

9.2.1 The Members agreed that having reviewed all the available relevant evidence with the benefit of up-to-date knowledge within the relevant specialisms, taking into consideration the limitations of the methodology of the time and the relative scarcity of evidence, a link between HPTs and congenital anomalies could not be concluded. Members were confident that all important scientific data had been identified, that a thorough review had been conducted, and that the process had been as transparent as possible.

9.2.2 Based on their extensive and thorough review of the evidence the Members concluded that, overall, they had found no convincing scientific evidence for an association between the use of HPTs during pregnancy and adverse outcomes (congenital anomalies, miscarriage and stillbirth). The Members considered there may have been a lack of transparency with how this issue had been assessed in the past and that this was most unlikely to happen under the current regulatory system.

9.2.3 The Members commented how moving and worthwhile it had been to hear the personal experiences of the families involved.

9.2.4 The Members acknowledged that many lessons have been learnt from the past and that regulation had been strengthened significantly since HPTs were on the market.

10. Recommendations of the Members

10.1 The Members discussed the following ideas for recommendations, acknowledging that, due to time constraints, these would need to be further developed further:

1. Consideration given to offering genetic testing for the families involved.
2. Strengthen ways to collect data on, and monitor the safety of, medicines used during pregnancy and consider how this could be taken forward. This should include:
    I. making use of the systems currently available and exploring ways of data linking, to enable exposure to medicines in pregnancy and adverse outcomes in the offspring (including miscarriage, congenital anomalies and mental or physical developmental disorders) to be identified
    II. routine surveillance of congenital anomaly databases
    III. access to data for researchers.
3. MHRA to continue collaborating with stakeholders in the healthcare sector to improve communication of safety messages to healthcare bodies and implementation of measures to manage risk.
4. Use of non-clinical data to understand better mechanisms of drug-induced injury.

11. Next Steps

11.1 Members were advised they would be sent a draft report to review in late June and any outstanding issues could be discussed at a meeting in early July, as necessary. An updated report would then be sent to members and invited experts on the Group.

10. Any Other Business/Meeting Close

10.1 Actions:

- The Group requested to receive a copy of Mrs Lyon's presentation notes.
- The Group requested to receive the documents mentioned by Dr Petersen relating to studies published in JAMA on exposure of antidepressants in pregnancy and a range of adverse pregnancy and child outcomes such as preterm birth and autism.

10.2 The meeting closed at 17:03.

COMMISSION ON HUMAN MEDICINES - HORMONAL PREGNANCY TESTS WORKING GROUP (HPTWG)

MEMBERSHIP OF THE HPTWG AND INTERESTS DECLARED

Chair	**Interests declared**
Dr Ailsa Gebbie	None
Members	**Interests declared**
Mr Ian Currie	None
Professor Pat Doyle	None
Mrs Joyce Epstein	None
Professor Stephen Evans	LSHTM as a whole receives funding in several departments (including medical statistics) from various pharmaceutical companies, including GSK. I am not responsible for, funded by, or have any of my own research funded by any company. In spite of this and because there is a GSK-funded chair in the department I work in, though I have no involvement in this whatsoever, GSK is regarded as a company where I have a C of I by the EMA. I find this bizarre in that GSK funds more of the work of the EMA as a whole in a very direct manner yet I am regarded as being conflicted, yet they are not. GSK ceased funding a chair in medical statistics about two years ago (I am not involved and do not know the exact date). The holder of that chair has retired. LSHTM as a whole receives funding in several departments (including medical statistics) from various pharmaceutical companies as I imagine is the case in every UK university doing medical research. I am not responsible for, nor funded by, nor have any of my own research funded by any company.
Professor Joyce Harper	I attended a conference in Taiwan in 2009 that was hosted by Schering Plough Taiwan Ltd Organon Women's Health & Fertility. I was only there for one night. I gave a talk and came straight back. They paid my travel but I did not get any income from it. The conference was

	about fertility and had nothing to do with HPTs. Also I do not think this is a conflict but I think we should also acknowledge that I run a public engagement group to discuss women's health issues – www.globalwomenconnected.com. I write articles that are open to the public but I have never written anything about HPT.
Professor Dr Axel Heep	None
Professor Stephen Hillier	I delivered lectures at international scientific meetings sponsored by Organon or Schering, as follows: Cellular Aspects of Preovulatory Folliculogenesis in Primate Ovaries Symposium to mark the 50th anniversary of Organon France September 1987, Paris, France. Follicular Function in Polycystic Ovaries Symposium on 'Chronic Hyperandrogenic Anovulation' October 1989, Oss, The Netherlands. Are estrogens of importance to ovarian function? Ernst Schering Research Foundation Workshop 46: New Molecular Mechanisms of Estrogen Action and their Impact on Future Perspectives in Estrogen Therapy March 5-7 2003, Berlin, Germany. As a PHD student (1972-1975), I participated in the development of assay methods for Norethindrone Acetate and Norgestrel, resulting in the following publications: Hillier, S.G., Jha, P., Griffiths, K. & Laumas, K.R. (1977) Long-term contraception by steroid-releasing implants. VI. Serum concentrations of Norethindrone in women bearing a single silastic implant releasing Norethindrone acetate. Contraception 15: 473-488. Thomas, M.J., Danutra, V., Read, G.F., Hillier, S.G. & Griffiths, K. (1977) The detection and measurement of D-Norgestrel in human milk using Sephadex LH-20 chromatography and radioimmunoassay. Steroids 30: 349-361.
Professor Alison Macfarlane	I have had no direct involvement or remuneration from any of the companies below. The one

	question I can't answer definitively, but will check is that I have a portfolio of shares managed by my bank and I never know at any one time what shares I have. I have told them types of companies I don't want my money invested in and pharmaceuticals may or may not be on this list. I will get back to you, but I have never consciously bought shares in any of those companies.
Ms Sara Payne	None
Mrs Farrah Pradhan	None
Professor Shirley Price	Previous non-personal, non-specific interest with Bayer. Recently attended a SafeScIMet Executive Committee meeting where the taxi fare and dinner expenses were paid by Bayer. The monies have now been paid, so interest no longer exists. At the University of Surrey as part of my job specification I have organised and taught on a Master's/CPD programme in Applied Toxicology (1996-2014) which was designed to educate and train scientists in the field of Toxicology. This programme attracted delegates and guest lecturers from Pharma Industries, Academia, Agrochemical and Chemical Industries, Cosmetic Industries and Regulatory Authorities. Of the companies listed above GlaxoSmithKline, Pfizer and Sanofi sent students/delegates to attend modules either for CPD or to gain an academic qualification. Members of staff also lectured on the programme from these three companies. The delegates paid a tuition fee to the University of Surrey for attendance to the one week modules.
Professor Siobhan Quenby	None. I received a fee for a lecture from Ferring.
Dr Richard Quinton	None
Dr Connie Smith	I can confirm that I have/had no personal interests in the companies who developed and marketed HPTs, or their predecessors. I have had no involvement in these products.

Professor Michael D Threadgill	I have no current conflicts of interest for any of the companies and other bodies concerned and I have not been involved in in any campaigning or strong opinions in this area. For the sake of completeness, I declare that my research group collaborated with and received a small (approx. £2000) amount of research funding from Sterling Winthrop 1992-1995 on a project to assay theophylline in biosamples for patients being treated for asthma and related disorders (nothing to do with pregnancy testing); part of Sterling Winthrop went on to become part of Sanofi a few years later. This relationship ceased over twenty years ago when the project ended.
Dr Diana Wellesley	I have no conflicting interests
Invited Experts	**Interests declared**
Professor Leon Aarons	Departmental research funding in Pfizer. This is generic funding for our academic research and pertains mainly to drug metabolism. I have never worked with HPTs.
Mr Nick Dobrik	None
Professor Helen Dolk	My institution (Ulster University) has had a recent research grant from GlaxoSmithKline UK ending in March 2014, on the subject of antiepileptic drug safety in pregnancy. I was the principal investigator. For a 6 month period in 2010, I was co-investigator on a project regarding maternal age and neural tube defects funded by Bayer. Funding again went to Ulster University as a research grant. I have no personal interests in any of the companies listed. As part of the EUROmediCAT project, funded by EU FP7, we conducted a signal generation study looking for associations between specific congenital anomalies and any medications used during pregnancy, in data covering the period 1995-2011. This has recently been published (Given J, Loane M, Luteijn J, Morris J, de Jong-van den Berg L, Garne E, Addor M-C, Barisic I, de Walle H, Gatt M, Klungsoyr K, Khoshnood B, Latos-Bielenska A, Nelen V,

	Neville A, O'Mahony M, Pierini A, Tucker D, Wiesel A and Dolk H (2016). EUROmediCAT Signal Detection: An Evaluation of Selected Congenital Anomaly-Medication Associations. British Journal of Clinical Pharmacology. DOI: 10.1111/bcp.12947). The medications examined did NOT include HPTS but included the contraceptive levonorgestrel/ethinylestradiol, pregnen (4) derivatives and pregnadien derivatives and synthetic ovulation stimulants. We are currently preparing to follow-up the results with more in depth study, again NOT in relation to HPTs for which we have no data.
Professor Kay Marshall	I can confirm that at this time I receive no remuneration in any form from the companies you list. I have never given any of these companies advice on the safety of their products. In the past (over ten years ago) I have collaborated with Bayer and GSK but the laboratory based projects were focused on compounds that may have had potential to prevent uterine hypercontractility and so had potential in the management of conditions such as pre-term labour.
Dr Irene Petersen	Has recently taken up part time appointment at Aarhus University, Denmark as professor in biostatistics. Academic members within that department receive funding from Pfizer in New York.
Dr Christof Schaefer ***(participation ceased on 22/4/216)***	I have published a retrospective observational study on birth defects and HPT and within the discussion of this publication I have expressed an opinion. [Tümmler G, Rißmann A, Meister R, Schaefer C. Congenital bladder exstrophy associated with Duogynon hormonal pregnancy tests - signal for teratogenicity or consumer report bias? Reprod Toxicol 2014; 45: 14-19.] I gave advice to German obstetricians on drug's risk and safety on a web based platform sponsored by Bayer Healthcare. Monthly royalty was 300 € paid by Bayer Healthcare. I cancelled the contract in September 2012. *Secretariat note: Legal advice was that this terminated consultancy contract would not necessarily preclude him from being on the Group as it was not a current personal interest.*

	However, due to the sensitivity of the issue the decision was taken that it would not be appropriate for Dr Schaefer to continue as an invited expert. Dr Schaefer was removed from the EWG on 22nd April 2016. At that time he had attended the first meeting only, at which no scientific evidence was presented.
Professor Faith Williams	I own some shares in GlaxoSmithKline plc which are held through a nominee company of HSBC bank plc. I do not have shares in any of the other companies listed or have had any other interests in the companies which originally marketed HPTs. I received non personal research funding from Pfizer for a member of staff in my team at Newcastle between 2004 and 2007.
Dr Laura M Yates	We (UKTIS) were commissioned by Prof Steve Robson to produce a written review (along the lines of the monographs that UKTIS writes for HCPs) of the literature published post 1982, on Primodos, OCs and Hormonal Pregnancy Tests. Prof Robson used our review of the published data to write a legal report for Peter Todd from Hodge solicitors who was acting on behalf of individuals with birth defects whose mothers were exposed to primodos and who were seeking to bring a claim against Bayer on the basis it was a pharmaceutical teratogen. I would be very interested in participating if you feel that the above does not preclude my involvement. I would be happy to share the review produced by UKTIS with you (in confidence) if that would be helpful. Unconditional funding from GSK and Baxter, the manufacturers of the two swine flu vaccines available in the UK during the 2009/10 H1N1 pandemic was provided to NUTH (the Newcastle upon Tyne Hospitals NHS Foundation Trust) to support the extension of an existing NIHR HTA funded study - 'H1N1 in Pregnancy Study' - to include the collection by UKTIS of observational prospective outcome data on women vaccinated during pregnancy with the influenza vaccines, Pandemrix (GSK) and Celvapan (Baxter). I can confirm that the information on our 'bumps' website is in essence a summary of what UKTIS produced for Professor Robson, and which I informed the MHRA of at an early stage. I

	received no personal remuneration for the work. A fixed fee was paid to UKTIS to undertake the work, but was less than the 'true' cost the report - if the staff time spent is used to calculate the cost, and could therefore be seen as having a part- voluntary contribution which is reflected in the unpaid/uncompensated overtime that members of UKTIS provide (of their own volition) on a regular basis. *Secretariat note: The above was declared by Dr Yates prior to her appointment to the Group, then clarified again during the review, This was discussed by the Group, which agreed that her status as an invited expert, with the limitations that came with that category of participation, was appropriate.*
Observers	**Interests declared**
Mrs Marie Lyon	Has engaged in media activity relating to HPT's prior to receiving invitation.
PD Dr Elke Röhrdanz	Works as a preclinical assessor at the German Federal Institute for Drugs and Medical Devices and may have access to preclinical data concerning HPTs.