Medicines & Healthcare products Regulatory Agency

MHRA

Ms Joanna Wood
Review Team
Independent Medicines and Medical Devices Safety Review
King's College,
London
SE1 1UL

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Medicines and Healthcare products Regulatory Agency

10 South Colonnade
Canary Wharf
London
E14 4PU
United Kingdom

+44 (0) 20 3080 6000

gov.uk/mhra

Dear Ms Wood

Thank you for your letter of 24 May enclosing a transcript from the evidence given to the review by the All-Party Parliamentary Group (APPG) for Hormone Pregnancy Tests (HPTs).

I am grateful for the opportunity to respond. Annex 1 sets out our response to the points where our position differs from that of the APPG.

Since the MHRA provides the Secretariat to the Commission on Human Medicines (CHM) and Expert Working Groups (EWG), Dr Ailsa Gebbie (Chair of the EWG on HPTs) and Professor Stuart Ralston (Chair of CHM) have asked us to respond to process-related points in the transcripts they have each been sent. These are also included in Annex 1.

I would also refer you to my letter of 24th April for our position on how conflicts of interest of experts are managed and to our written response to the call for evidence submitted on 31st October 2018 for clarification of the Agency's funding model.

I would be happy to provide any further clarification, if that would be helpful.

Yours sincerely

June M. Raine

Dr June Raine
Director – Vigilance and Risk Management of Medicines

T [redacted]
E [redacted]

Annex 1 – points where MHRA disagrees with the transcript

Passage 1

The original CHM EWG review on HPTs

Responses to several points made about the original review of the CHM EWG on HPTs are provided below.

Review of regulatory failings

The CHM EWG on HPTs was established to conduct a review of the scientific evidence on the association between HPTs and adverse outcomes in pregnancy and accordingly comprised experts in the relevant specialisms. It was made clear on several occasions that this review would not be looking into possible past regulatory failures.
The draft terms of reference were confirmed by the Minister in a letter to the Chair of the APPG in September 2015 where the Minister further explained that this would be a review of the scientific evidence to establish whether there is any causal association between use of HPTs and subsequent birth defects in the child.

Review of all the evidence

The Group was established to conduct a scientific review and all scientific evidence sent to or gathered by the MHRA was summarised, presented to the EWG and subsequently published.
To ensure the EWG were cognisant of the background to the review, MHRA also provided professional translations of all documents from the Landesarchiv Berlin and all documents identified by a professional researcher from the National Archives. A chronology of events and schedule of documents which summarised much of this information was also presented to the Group on a number of occasions. All these documents have been published.

Transparency

Under the Human Medicines Regulations 2012, restrictions are expressly placed on the disclosure of any information by a person who obtains it by virtue of those Regulations. This includes those participating in meetings of the CHM and its Expert Working Groups. All participants of the Group were required by the MHRA to sign a confidentiality declaration prior to their participation, to confirm their understanding that the paperwork, any other correspondence and discussions of the Group were strictly confidential and not to be disclosed.

There was no particular or unusual treatment for Mrs Lyon compared to other members of the EWG or compared to other Groups that have operated in similar ways.

Mrs Lyon was informed in November 2017 that she was free to discuss her involvement in the process and, in line with the Government's commitment to publish the report of the review and all the evidence considered by the Group in full, all documents were also made available for public scrutiny at that time.

Peer review of the report of the CHM EWG on HPTs

The MHRA does not arrange for peer review of the reports of Expert Working Groups of the CHM. As the body that established the EWG to review the scientific evidence on HPTs and adverse outcomes of pregnancy the CHM peer reviewed the report provided to it by its EWG, as would be the case for any Expert Group report.

The Group's findings and its draft report were considered by the CHM in October 2017 together with a statement from the Chair of the Association for Children Damaged by HPTs, who was invited to the CHM meeting. The Commission considered that the EWG had conducted an extensive and thorough review of

the available evidence with the benefit of up-to-date knowledge, and endorsed the conclusions of the review.

The Commission also considered that Mrs Lyon had highlighted some areas of the draft report that could be open to misinterpretation and would therefore benefit from clarification. The CHM advised that it would be important to ensure that the points made by Mrs Lyon in her statement were carefully considered before finalisation of the report. At the following meeting in November 2017, the CHM was satisfied that all the necessary clarifications had been made and endorsed the report, its findings and recommendations.

As the CHM is responsible for establishing its Expert Working Groups, and is itself comprised of high calibre scientists of national and international standing, it is appropriate that the Commission is also responsible for peer reviewing the outputs of its Groups. Nevertheless, the MHRA will consider carefully any recommendations made by the Review on the peer review process.

Passage 2

The publication by *Heneghan et al.*

Responses to a number of points which have been made by the APPG for HPTs about the expert review of the publication by *Heneghan et al.*, are provided below. To clarify, in order to ensure that the ad hoc Expert Group established to look independently at the new publication was not biased in any way by knowledge of the previous review, Professor Stephen Evans was not involved in this ad hoc Expert Group review and neither the terms of reference of the Group nor any information presented to them detailed the previous review of the original EWG.

Findings of the CHM and EMA reviews of *Heneghan et al*

The independent reviews of the CHM Expert Group and the European Committee for Medicinal Products for Human Use (CHMP) did not contradict the findings of the meta-analysis by *Heneghan et al.* What they both concluded, was that the analysis could not be considered robust due to the variable quality of the original studies included in it and to a number of methodological concerns, outlined in the published minutes.

Destruction of the recording of the EWG discussions

To ensure transparency, encourage full and frank discussion and eliminate disagreements over finalisation of the minutes, Expert Group meetings are now recorded on the full understanding and agreement of all present that they will be destroyed once the minutes have been agreed.

Two main experts were not epidemiologists

The two main experts on the Group responsible for evaluating the publication by *Heneghan et al.,* were Professor Julian Higgins, Professor of Evidence Synthesis and Director of Research at the Department of Population Health Sciences at the University of Bristol[1] and Professor Jonathan Sterne, Professor of Medical Statistics and Epidemiology at the Bristol University[2].

Professor Higgins has led or contributed to over 400 publications, most of which are on meta-analysis methodology, and was co-developer of the ROBINS-I tool and co-editor of the Cochrane Handbook for Systematic Reviews of Interventions.

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[1] http://www.bristol.ac.uk/social-community-medicine/people/julian-p-higgins/index.html
[2] http://www.bristol.ac.uk/social-community-medicine/people/jonathan-a-sterne/index.html

Professor Sterne's areas of research include epidemiology, meta-analysis and systematic reviews, and causal inference and he is also co-developer of the ROBINS-I tool and co-author of the Cochrane Handbook for Systematic Reviews of Interventions.

The Cochrane Handbook for Systematic Reviews of Interventions does not mandate use of ROBINS-1 and refers to NOS as an alternative option. However, the Group raised concerns over the way in which NOS was applied in the *Heneghan et al* meta-analysis.

To my knowledge the work on ROBINS-I was supported by a grant from the Cochrane Methods Innovation Fund (2011) and by Medical Research Council (MRC) grant MR/M025209/1.