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1st May 2019

Joanna Wood
Lawyer to the Review
Independent Medicines and Medical Devices Safety Review
King's College, London
Shepherd's House
Room 3.24
London SE1 1UL

Dear Ms Wood

Thank you for your letter of 12 April, giving the Expert Working Group (EWG) on Hormone Pregnancy Tests (HPTs) the opportunity to respond to comments made by the Chair of the Association for Children Damaged by Hormone Pregnancy Tests (Mrs Marie Lyon) in evidence she gave to the Review. I apologise for the slight delay in responding.

A number of the comments in the transcript relate to the procedures followed in running the EWG or to broader points about medicines regulation. The MHRA has addressed these separately as they provided the secretariat support for the Group. I have responded to comments which were specific to the deliberations or conduct of the EWG.

The conclusions of the EWG report are unequivocal for 'no association'

In Passage 1 of her testimony Mrs Lyon says that the conclusion of the report of the EWG is that there was no association between HPTs and adverse effects and that this conclusion was absolutely unequivocal. The Group was very careful not to conclude that there was definitely no causal association between HPTs and anomalies. What we did conclude was that the evidence we reviewed did not support the association as being causal and this is quite different. Unfortunately, the semantics of language around this issue have distracted from the Group's findings and conclusions.

The data studied in depth by the Group were generally of very poor quality compared to today's standards which is what we have to judge it against. While certain aspects were slightly more persuasive of a possible weak association, when these were considered in the context of the complete body of evidence, there were sufficient doubts about their reliability to lead us to draw the conclusion we did: that overall the data do not support the association as being causal.

It is possible that new data may emerge that suggest different findings, and in this regard, I am aware that the MHRA is totally committed to reviewing any relevant new data that become available.

Extent to which as Chair I allowed Mrs Lyon to contribute to the EWG

In Passage 1 of her testimony, Mrs Lyon refers to my statement that I invited her to comment after every EWG meeting. As Chair of the EWG I was provided with guidance on how to conduct the meeting, with the categories of attendees (member, invited expert, observer) and the level of contribution that was expected for each category. This guidance had been drawn up by the MHRA to ensure that the independence of the EWG was maintained and that no one who had a real or perceived conflict of interest could unduly influence the discussions. This guidance was provided to each participant with the declaration of interest form and is standard policy. I attach a copy for reference.

As Chair of the Association for Children Damaged by Hormone Pregnancy Tests, Mrs Lyon had the category of Observer which meant being invited to all meetings, receiving all papers and presentations and being able to respond to questions from me or from the members as necessary. After Mrs Lyon complained to the MHRA that she, as an observer, was unable to contribute, it was agreed that, as a special arrangement, she would be offered the opportunity to comment after every discussion item, and I specifically invited Mrs Lyon to do this. All Mrs Lyon's contributions are noted in the published minutes, which were agreed by the EWG.

My response to Mrs Lyon saying she would withdraw from the review

In November 2017, Mrs Lyon threatened to leave the private briefing meeting that was organised by the MHRA for EWG members to discuss the findings and recommendations of the review with the families who were members of the Association, many of whom had provided evidence. I understood Mrs Lyon's position but thought that as she had been part of the review throughout, it would be a pity to withdraw at this stage and so encouraged her to stay, which she did. I do not recall Mrs Lyon saying she would withdraw at any time during the review or failing to reply to any of her letters.

Statements made that an association between HPTs and adverse pregnancy outcomes cannot be ruled out

In Passage 2 (paragraph 1) of the transcript, Mrs Lyon quotes from the EWG's oral evidence to the Review and says that what was said in evidence to the review was contrary to the conclusions of the report and contrary to statements made by me to Sky News.

The issue in question is the difference between an 'association' between a medicine and an adverse reaction and a 'causal association'. We have consistently said that the Group's overall conclusion was that the available scientific evidence, taking all aspects into consideration, did not support a 'causal' association between the use of HPTs, such as Primodos, during early pregnancy and adverse outcomes, either with regard to miscarriage, stillbirth or congenital anomalies.

Mrs Lyon returns to this point in passage 6 of her testimony, where she says that it is difficult to understand that the clear majority of epidemiological studies demonstrated an association but were not accepted as credible evidence of an association. Mrs Lyon goes on to say that proving causality is virtually impossible.

Turning to Mrs Lyon's comment that proving that a drug caused an adverse reaction is unusual, there are some good examples of cases where there is sufficient evidence to be satisfied that there is a causal association. Examples might include ototoxicity with aminoglycosides, hypersensitivity reactions with abacavir, or oculomucocutaneous syndrome with practolol. As discussed above, it is the role of the government's expert advisory group to weigh up the available evidence and reach a conclusion as to whether or not it supports a causal association.

Professor Evan's statement about women who took HPTs

During his oral evidence Professor Evans explained one of the main confounding factors affecting the epidemiological evidence (which is evidence at a population level), is that women who sought or were offered pregnancy tests at the time that HPTs were available were likely to be different in some way from the majority of women who went through pregnancy without having a test. In any research study this issue would be a potentially significant source of confounding.

Professor Evans was commenting on studies like the one by Torfs et al (1981), which found that in general women who had a pregnancy test of any kind (ie not just HPTs) had a higher percentage reporting a previous fetal loss or who were over the age of 40 years compared to those in the untested population. A plot of cumulative probability of fetal death for the groups of women who had a HPT was no higher than the rates for those who had a urine pregnancy test or a serum pregnancy test. However, the rates of fetal

loss for all three pregnancy test groups were higher than those for the women who were not tested, suggesting a difference in risk of those receiving and those not receiving a test.

Attendance at the EWG by a representative of the German Regulatory Authority (BfArM)

After I was informed by the MHRA of a request from the German regulatory authority (BfArM) I agreed that the Head of Genetic and Reproductive Toxicology at BfArM could attend the meeting as an observer. The BfArM representative maintained observer status and did not make any contribution or speak at any time during the review meetings.

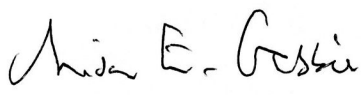
The Terms of Reference of the Expert Working Group

In Passage 6 of her testimony, Mrs Lyon makes reference to the difficulties of determining causality and says 'That's why it was changed'. I assume by this Mrs Lyon is referring to the Terms of Reference of the EWG.

The EWG Terms of Reference were not changed. The Terms of Reference defined the scope of the review as needing to take into consideration all evidence on the possible association, which was already known, between HPTs and adverse pregnancy outcomes. What the terms of reference did not set out to do was dictate the conclusion of the group on the nature of that association – the terms of reference were simply framed in this way to ensure that the totality of the evidence on any strength of association was considered. It is my clear understanding that the Expert Working Group was formed specifically to review all the available evidence and resolve the long-standing question on the nature of the association that was observed in some studies. It is my firm belief that my Group fulfilled these Terms of Reference in a scientifically rigorous, objective and independent manner.

I hope that this provides clarity on the issues raised in Mrs Lyon's testimony relating to the deliberations of the EWG. Thank you again for giving us the opportunity to respond.

Yours sincerely



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