EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Ms Joanna Wood
Review Team
Independent Medicines and Medical Devices Safety Review
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EMA/369470/2019

Dear Ms Wood

Independent review of testimony from Association of Children Damaged by Hormone Pregnancy Tests

We are grateful to you for an opportunity to contribute to your review by addressing Marie Lyon's comments about our work (your emailed letter of 26 June 2018).

The MHRA asked the Committee for Medicinal Products for Human Use (CHMP)[1] in 2018 to provide its opinion on two scientific matters relating to hormone pregnancy tests. These two requests were made under Article 5(3) of Regulation (EC) No. 726/2004; this procedure ('Article 5(3) referral') is used for seeking CHMP's opinion on scientific matters relating to the evaluation of medicines for human use. Although hormone pregnancy test products have been off the market for many years, the CHMP considered the reviews relevant because the products' ingredients – ethinylestradiol and norethisterone – are present in currently marketed medicines.

The first Article 5(3) referral concerned a zebrafish study[2] for evaluating ethinylestradiol and norethisterone in human pregnancy (procedure EMEA/H/A/-5(3)/1470). The second referral concerned a meta-analysis[3] on oral hormone pregnancy tests and risk of congenital malformations (procedure EMEA/H/A/-5(3)/1477).

In Passage 1 of your transcript, Marie Lyon asserts that the European Medicines Agency (EMA) "did not even ask to meet Professor Vargesson, and based their results on the information provided by the [UK] Commission on Human Medicines". The CHMP's assessment report is a detailed evaluation of the zebrafish study which amply shows that this was an independent review, not reliant on the Commission on Human Medicines' previous conclusions. The scientific evaluation, led by CHMP members from the Netherlands and Sweden, was supported by relevant EU experts in methods for

[1] CHMP is a committee of the European Medicines Agency (EMA) with responsibility for assessing evidence on human medicines. It is supported by a medicines safety committee (PRAC) and scientific working parties such as the safety working party.

[2] Brown S, Fraga LR, Cameron G, Erskine L, Vargesson N. (2018) The Primodos components norethisterone acetate and ethinyl estradiol induce developmental abnormalities in zebrafish embryos. Sci Rep. Feb 13;8(1):2917

[3] Heneghan C, Aronson JK, Spencer E, Holman B, Mahtani KR, Perera R, Onakpoya I. Oral hormone pregnancy tests and the risks of congenital malformations: a systematic review and meta-analysis [version 1, updated 31 Oct 2018]. F1000Research 2018, 7:1725

evaluating medicines safety. To ensure the thoroughness of its evaluation, the CHMP sought — and obtained — from the corresponding author, additional details of the study not available in the published paper (see 'clarification provided' on page 12 of the assessment report).

At the end of Passage 1, in the context of a meta-analysis by Heneghan and colleagues, Marie Lyon states: "Once again the medicines agency did not speak to either Professor Heneghan or Dr Aronson". In fact, Professor Heneghan was informed of EMA's review of the meta-analysis (procedure EMEA/H/A/-5(3)/1477) and he very helpfully provided information to the CHMP, including published reports of old studies.

In Passage 2, Marie Lyon considers that the CHMP review of Heneghan and colleagues' "meta-analysis does not have public trust or confidence, and was clearly not transparent". The CHMP's assessment report, detailing the evaluation of the meta-analysis is in the public domain. This detailed scientific discussion should reassure readers of the robustness of CHMP's conclusions and recommendations.

Marie Lyon (Passage 3) implies that EMA's scientific evaluation is compromised by the previous and current roles of the CHMP chair. EMA takes great care to ensure that its committee members, scientific experts and staff do not have financial or other interests that could affect their impartiality (see EMA's webpage on handling competing interests). The CHMP is governed by rules of procedures to ensure the impartiality and robustness of its scientific assessment. The rules for referral procedures require, for example, two CHMP members to independently produce each an assessment report (in this case, from Sweden and the Netherlands for the first referral; from the Netherlands and Portugal for the second), review of this evaluation by the other CHMP members, discussion of the evaluation, and collegiate decision where all members of the committee vote. Importantly, the CHMP chair does not vote.

In passage 4, Marie Lyon says that EMA declined her written and telephoned request to participate as an observer at CHMP's review and that the EMA gave no reason for the refusal. Our records show that she contacted us (through the Ask EMA facility) on 23 July 2018. We wrote back to her on 2 August 2018 and during a further telephone exchange with her on 21 August 2018, we explained that, based on the review's scope, input from her organisation was not needed at this stage. However, we also informed Marie Lyon that if later needed, EMA would consult stakeholders.

We have not found records of any other exchanges with Marie Lyon.

In the last part of Passage 4, Marie Lyon considers that according to EMA, "there were no concerns for future use of the drug". This does not properly reflect the CHMP's conclusions. The CHMP reviews aimed to understand how the evidence relating to previously marketed combination of ethinylestradiol and norethisterone in hormone pregnancy tests affected the use of existing combinations of ethinylestradiol and norethisterone.

EMA's review on the zebrafish model concluded (*italics* added for the purpose of this response):

> "… the results of this study do not *add* to the current knowledge regarding adverse events in early pregnancy in human. The CHMP concluded that there are no *new* clinical implications [for the existing combinations of ethinylestradiol and norethisterone] based on the results of the presented zebrafish study"

The review on the meta-analysis concluded:

> "…the quality of most studies used [in the meta-analysis] is questioned and, as a result, the conclusions of the meta-analysis cannot be considered reliable … the conclusion that current clinical data available do not support a signal of teratogenicity of a combination of norethisterone/ethinlyestradiol remains valid"

We believe the critical comments about EMA's scientific reviews may have stemmed from a misreading of the scope of these reviews. We trust that our response will reassure you of the CHMP's careful and impartial approach to its scientific evaluation of evidence. As requested, we have confined our answers

to specific points raised by Marie Lyon. However, we would be only too happy to answer any other questions your review raises or to provide additional information on the two scientific reviews.

Yours sincerely,

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