



European Ombudsman

Emily O'Reilly
European Ombudsman

Mr Peter Gøtzsche

E-mail: pcg@cochrane.dk

Strasbourg, 26/06/2017

Complaint 1475/2016/JAS

Dear Mr Gøtzsche,

I write in relation to your complaint 1475/2016/JAS concerning the European Medicines Agency's (EMA) handling of the so-called referral procedure regarding a pharmaceutical product, Human papillomavirus (HPV) vaccines.

HPV vaccines prevent infections by certain types of HPV, which can cause, in particular, cervical cancer. The World Health Organization recommends that these vaccines should be included in all national immunisation programmes¹.

On 16 February 2017, I asked EMA for a reply to a number of questions related to your complaint. I also provided EMA with the additional background material submitted by you on 2 February 2017. Please find attached my request to EMA as well as its detailed reply.

You complained about an EMA "referral procedure" in which EMA's Pharmacovigilance Risk Assessment Committee (PRAC)² examined whether there is any causal association between HPV vaccination and two syndromes, complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS). PRAC concluded that the evidence does not support the

¹ <http://apps.who.int/iris/bitstream/10665/255353/1/WER9219.pdf?ua=1>

² The PRAC consists of a chair, elected by serving PRAC members, one member and an alternate nominated by each of the 28 EU Member States, one member and an alternate nominated by Iceland and Norway, six independent scientific experts nominated by the European Commission, one member and one alternate representing patients organisations nominated by the European Commission and one member and an alternate representing healthcare professionals nominated by the European Commission: http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/PRAC/people_listing_000112.jsp&mid=W00b01ac058058f328



view that there is a causal association between the HPV vaccines and these two syndromes.

As explained in my previous letters, the Ombudsman's Office is not a scientific body. It is not within my mandate to examine the merits of scientific evaluations carried out by specialised scientific services. In this context, I also note that you stated, in your complaint, that the "*complaint to the [O]mbudsman is not about whether the HPV vaccines do more good than harm.*"

In my role as Ombudsman, I may seek to assess whether EMA has procedural safeguards in place to ensure that the scientific advice it receives is as complete as possible and independent. The questions I have put to EMA are meant to obtain explanations and clarifications to that end. These questions are related to the arguments raised in your complaint regarding the following issues: (a) the referral procedure, (b) transparency and openness (c) alleged conflicts of interest.

If you wish to make any comments on EMA's reply or on the meeting report sent to you on 16 February 2017, please send them to me before **31 July 2017**.

I would appreciate if you could, when making your comments, take into account the annexed preliminary views of my inquiry team in relation to the concerns put forward in your complaint and EMA's explanations thereon. In this context I note that it is the view of my inquiry team that the explanations provided by EMA, either in response to your initial letter or in response to my request, were reasonable.

Based on EMA's reply and your comments thereon, I will decide on the appropriate next step in the inquiry.

Yours sincerely,

Emily O'Reilly
European Ombudsman

Enclosure:

- Annex - Preliminary views of the inquiry team
- Request for a reply sent to EMA in case 1475/2016/JAS
- Copy of the reply submitted by EMA in case 1475/2016/JAS



Annex - Preliminary views of the inquiry team

a. The safety referral procedure

The internal preliminary report

The complainants claimed that divergent opinions expressed by the PRAC co-rapporteurs³ in the internal preliminary reports were left out of PRAC's final, publicly available assessment report⁴.

EMA said that the opinions set out in the preliminary reports constituted "work in progress" and that these opinions could change as a result of the deliberations and discussions amongst the PRAC members. EMA noted that all opinions and points of view are discussed in the relevant committee and issues are resolved either during the plenary committee discussions or through consultation with other experts.

EMA said that any PRAC member (including any co-rapporteur) who continues to have reservations at the time of the finalisation of the procedure may raise those concerns by voting against the committee majority and expressing a divergent position. However, in the present case, the recommendations of PRAC were adopted by consensus.

The inquiry team concludes that, even if certain members expressed divergent opinions during the course of the procedure, they obviously considered these opinions to be properly addressed by the end of the procedure. This is evidenced by the fact that all members, including the co-rapporteurs, voted for the final recommendation adopted by PRAC.

Publication of the internal preliminary report

The Ombudsman asked EMA to consider making available more information on its assessments, including on any initial concerns expressed and on how these concerns are dealt with during the process.

EMA replied that differences in opinion are made publicly available in the final report if those differences persist until the adoption of the final report. However, if such preliminary views are not maintained at the end of the procedure, the publication of such information would give rise to confusion as to the final conclusions reached.

Nevertheless, any request for public access to documents containing preliminary views, such as the preliminary reports of the (co-)rapporteurs, are processed in accordance with EU rules on access to documents.

Generally, the inquiry team finds the explanations to be reasonable. All members of PRAC agreed with the final assessment report. The inquiry team

³ According to Article 6.2 of the PRAC Rules of Procedure the "role of the PRAC rapporteur is to prepare a recommendation or an advice, as applicable, together with an assessment report, if appropriate, on the relevant issue raised to the PRAC according to the timetable agreed for the procedure, taking into account the timeframe laid down in the relevant legislation" (available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/03/WC500139609.pdf).

⁴ Available at:

http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/HPV_vaccines_20/Opinion_provided_by_Committee_for_Medicinal_Products_for_Human_Use/WC500197129.pdf



considers, nevertheless, that the Ombudsman might consider suggesting to EMA that it should, in the future, explain **more clearly** to interested parties how differences in views are dealt with during the assessment of its scientific committees.

The “updated assessment report”

The complainants asked EMA to explain a number of statements made in an “updated assessment report”. This report appears to have been produced by one of the co-rapporteurs and is an update of that co-rapporteur’s internal preliminary report. The complainants argue that these statements show that criticisms made by that co-rapporteur were, later on, simply discarded by PRAC.

The inquiry team first notes that the statements in question were in fact made by Member State representatives on the PRAC. The complainants appear to mistake these statements as (allegedly discarded) criticisms made by the co-rapporteur. The inquiry team then notes that these comments were assessed by the co-rapporteur in the report and the co-rapporteur explains how these comments are addressed.

The Ombudsman’s inquiry team sees nothing untoward in this process, which reflects the normal course of scientific discourse, where questions are put forward and then addressed.

Consensus-based decision-making

The complainants suggest that committees that aim to reach decisions by consensus run the risk of being biased. The complainants base this assertion on their view that such committees often have one or two dominant people with strong views. The complainants claimed, in this context, that those on the committee who expressed concerns were pressured to agree to the consensus.

The inquiry team notes that striving for consensus in PRAC is expressly provided for by law⁵. Furthermore, the complainants have not put forward any evidence to suggest that participants were somehow pressured into adopting a certain point of view. Indeed, the Ombudsman’s inquiry team notes that the applicable rules **expressly permit** members of PRAC to record any divergent views they may have in the final assessment report. The Ombudsman’s inquiry team can therefore only conclude, on the basis of the evidence provided, that the fact that no PRAC member recorded any divergent views in the final report

⁵ Article 61a of Regulation 726/2004 on PRAC refers to Article 61(7), which states: “When preparing the opinion, each committee shall use its best endeavours to reach a scientific consensus. If such a consensus cannot be reached, the opinion shall consist of the position of the majority of members and divergent positions, with the grounds on which they are based.” (Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, OJ 2004 L 136, p. 1, consolidated version available at: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2004R0726:20120702:EN:PDF>)



was because any questions that PRAC members may have had at the beginning of the deliberations were adequately addressed during the deliberations.

Information provided by the Marketing Authorisation Holders (MAHs)

The Ombudsman asked EMA whether the raw data, analyses and explanations on the methodology applied, including those originating from the MAHs, are made available to all members of PRAC.

EMA confirmed that, in line with standard practice, all documentation submitted in the context of the referral procedure was made available to all PRAC members.

The inquiry team notes that the explanations provided appear reasonable.

MAHs' analyses of adverse events

The Ombudsman also asked EMA a number of questions on the difference between the two MAHs involved concerning the number of post marketing safety reports not meeting the criteria for the syndromes under investigation.

EMA provided possible explanations for the observed differences. In particular, EMA explained that all individual post marketing safety reports were provided to PRAC and reviewed by the (co-)rapporteurs. Regarding the concerns expressed by one Member State during the procedure, EMA stated that the Member State's PRAC member ultimately agreed with the final assessment report after deliberating in PRAC.

The inquiry team notes that the explanations provided appear reasonable.

Search strategies for undiagnosed adverse events

The complainants expressed disagreement with the "common search strategies" used to identify possible cases of undiagnosed CRPS and POTS.

The inquiry team notes that the Ombudsman's Office is not a scientific body. Thus, the inquiry team takes no view on the question of whether the search terms used by the MAHs are scientifically appropriate.

Pooling of placebos

The Ombudsman asked EMA to explain why PRAC considered it appropriate for the MAHs to pool the safety data of different clinical studies that used different types of placebos.

EMA explained that the pooling was considered appropriate despite the different placebos in order to gather the *overall* number of cases of POTS and CRPS for the purpose of detecting the potential existence of a safety signal. The incidence of both syndromes was very low, both in the vaccinated group as well



as in the placebo groups. The low incidence was in fact in line with the estimated incidence of such conditions in the general unvaccinated population.

While the inquiry team takes no view on the scientific aspects of this question, it notes that the explanations provided are logical and appear reasonable.

“Observed vs expected analysis”

The complainants also criticised the reliance on the so-called “observed versus expected” (O/E) analysis, where the number of reported cases is compared with the number that would be expected to have occurred naturally in the target population.

EMA has expressly stated that this analysis cannot determine causality. However, it can be useful in “signal validation”, that is, the process of evaluating data that might suggest a causal association between a medicine and an adverse reaction. PRAC had, in this context, concluded that in the O/E analysis, the rates of CRPS/POTS in vaccinated girls **were consistent with expected rates in these age groups**, even taking into account a wide range of scenarios regarding underreporting.

The complainants criticised this approach, arguing that analyses based on expected incidence were grossly unreliable.

The inquiry team takes no view on the scientific aspects of this question. However, it notes that the explanations provided are logical and appear reasonable. Importantly, the inquiry team also notes that it appears that all parties involved in the assessment were fully aware of the technical limitations of the available data. Thus, there is no suggestion that this data was misrepresented.

EMA’s literature searches

The Ombudsman asked EMA to explain why its literature search strategies are removed from the preliminary reports.

EMA explained that the search strategies were made available to all scientific experts involved. EMA confirmed that, in principle, literature search strategies are not confidential information and are therefore not redacted from the relevant documents when it receives a corresponding request for public access. However, EMA acknowledged that when it processed a request for access to the preliminary reports concerning the present procedure, the search strategies had been inadvertently deleted.

The inquiry team suggests that if the complainants remain interested in EMA’s literature search strategies, they may make a request for public access, taking



into account EMA's statement that such information is usually not considered confidential.

Drafting of the final report

The Ombudsman asked EMA to explain who drafts PRAC's final assessment reports.

EMA explained that in this case, in line with standard procedure⁶, the rapporteur with the assistance of the EMA Secretariat prepared the draft of the final PRAC assessment report which was subsequently commented upon and adopted by all members of PRAC.

The inquiry team notes that the explanations provided appear reasonable.

PRAC's comments on the research/data from Dr B. and the Uppsala WHO Monitoring Centre

The complainants argued that the final assessment report contained inappropriate comments concerning the research conducted by Dr B. They state that these statements come close to an accusation of scientific misconduct against Dr B.

The Ombudsman's inquiry team first notes that EMA argued that nothing in PRAC's position was intended to be construed as pejorative or an accusation of misconduct (against Dr B.).

The complainants further criticised how the PRAC presented and analysed the work of Dr B. and the Uppsala WHO Monitoring Centre. The complainants argue that PRAC's approach was unscientific and involved "cherry-picking".

The inquiry team notes that the comments in PRAC's final assessment report are points of view on the scientific value of the assessments by Dr B. and the Uppsala WHO Monitoring Centre. The Ombudsman's Office is not in a position to evaluate the science behind the views of PRAC. However, the Ombudsman's inquiry team notes that, as a general rule, PRAC must be able to take a view, on an issue of science, even if that involves calling into question hypotheses put forward by scientists.

Need for more research

The Ombudsman asked EMA to confirm that it will continuously evaluate any new evidence and will continuously examine if more specific research needs to be requested in the future.

In response, EMA provided explanations on its efforts to monitor and analyse pharmacovigilance data. It also described the obligations imposed on the MAHs concerning HPV vaccines, as well as the recommendations made by PRAC following the referral procedure.

The inquiry team notes that the explanations provided appear reasonable.

⁶ Article 6.2 of the PRAC Rules of Procedure.



b. Transparency and openness

Confidentiality clause

The Ombudsman suggested to EMA that it consider adapting its standard confidentiality clause for experts so that it reflects EMA's position that "*experts who disagreed with a collegial decision may discuss their disagreement in public, provided that they make clear that the views expressed are their own and not the view of the committee*".

EMA stated that it had initiated a review process of the template to that end, which was currently ongoing.

The inquiry team thus considers that EMA is in the process of addressing this point and that it should be asked to inform the Ombudsman's Office of the outcome of this process.

Access to documents

The Ombudsman also suggested that EMA could consider making publicly available lists of all relevant documents in its possession related to a specific referral procedure. This would enable citizens to make specific requests for public access, should they wish to obtain a document. Thereby, both the requester and EMA would need to spend less time on unnecessarily broad requests.

EMA did not address this suggestions in its reply. The inquiry team thus considers that this suggestions should again be put to EMA, either during the inquiry or when closing the inquiry.

Requested meeting minutes

The complainants requested public access to the minutes of the expert group consulted by PRAC during the referral procedure (the Scientific Advisory Group on Vaccines or SAG-V). EMA provided the complainants with a copy of these minutes. However, the complainants expressed concerns because some parts of these minutes had been redacted by EMA.

The inquiry team notes that the redacted information concerns the names of EMA support staff only (EMA disclosed the names of the PRAC rapporteurs/assessors and of its senior staff mentioned in these minutes). EMA expressly stated that it would not redact names of any scientific experts and of EMA staff with managerial and official functions.

The inquiry team is of the opinion that the decision to redact the names of EMA support staff, but not the names of other relevant persons, was reasonable. EU law defines "personal data" as "*any information relating to an identified or identifiable natural person*"⁷. The name of an individual clearly constitutes such information. The Ombudsman's inquiry team notes that there is no necessity to

⁷ Article 2(a) of Regulation (EC) No 45/2001 of the European Parliament and of the Council of 18 December 2000 on the protection of individuals with regard to the processing of personal data by the Community institutions and bodies and on the free movement of such data, OJ 2001 L 8, p. 1, consolidated version available at: <http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1496328094628&uri=CELEX:02001R0045-20010201>



disclose personal data of staff members who provide secretarial support (as compared to, for example, staff with managerial or scientific functions).

c. Alleged conflicts of interest

Availability of declarations of interest on the EMA website

The complainants had concerns that the declarations of interests of two SAG-V members were missing from EMA's online expert database⁸. The Ombudsman asked EMA to provide her with copies of these two declarations of interests.

EMA has now explained why these declarations were absent from its database. The reasons were purely administrative (the declarations in question had expired and had been removed from the database when the complainants attempted to access them). EMA has provided the two documents as an annex to its reply.

The inquiry team thus considers that EMA has settled this aspect of the complaint.

EMA's analysis of alleged conflicts of interest

The complainants criticised how EMA evaluates conflicts of interest. Apart from criticising EMA's general policy on conflict of interest, they called into question its assessment of the independence of certain members of the SAG-V.

The Ombudsman's inquiry team notes, by way of background, that EMA's conflict of interest policy has since been updated⁹.

The Ombudsman's inquiry team, however, has carefully assessed the cases referred to by the complainants. The Ombudsman's inquiry team took the following into account:

- any SAG-V expert that had declared to EMA that she or he had current financial interests (for example shares) in any pharmaceutical company, and any expert that had declared other interests linked specifically to HPV vaccines, was not allowed to participate in the final conclusions of the SAG-V meeting on HPV vaccines;
- concerning the declaration of the chair of the SAG-V, that he previously carried out, for the MAHs, research work on vaccines **other than the HPV vaccine**, the inquiry team does not agree that this fact gives rise to any conflict of interest. There is no evidence that this research work established any form of dependence of the person concerned vis-à-vis the producers of HPV vaccines. There is also no evidence that the research on other vaccines had any link to the subject under discussion, which was the safety of the HPV vaccine.

Regarding the complainants' argument that public statements made by some experts in support of HPV vaccines indicate bias on their part, the Ombudsman's inquiry team notes that it is not unusual for an expert involved in a scientific assessment to express opinions publicly on scientific subjects that

⁸ Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/landing/experts.jsp

⁹ The new policy is available at:

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/11/WC500216190.pdf



may be discussed. Such statements do not imply that a person is biased or that the positions they take in the scientific committees are not based on objective considerations only. Rather, the statements simply reflect the fact that the experts work in the relevant area of science and have developed scientific views on that area of science.

The inquiry team thus considers that EMA's explanations on this point are reasonable.