



European Ombudsman

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Strasbourg, 16/10/2017

Decision in case 1475/2016/JAS on the European Medicines Agency's handling of the referral procedure relating to human papillomavirus (HPV) vaccines

Dear Mr Gøtzsche,

On 10 October 2017, together with Karsten Juhl Jørgensen, Tom Jefferson, Margrete Auken, MEP, and Louise Brinth, you submitted a complaint to the European Ombudsman against the European Medicines Agency (EMA) concerning EMA's handling of the referral procedure on human papillomavirus vaccines

After a careful analysis of all the information submitted to me, I have decided to close my inquiry with the following conclusion:

There was no maladministration by the European Medicines Agency in the handling of the referral procedure on HPV vaccines.

The Ombudsman asks the European Medicines Agency to inform her of the final outcome of its review of the "Confidentiality Undertaking template".

I have also made the following suggestions to EMA:

That the Agency continue to explore ways to explain to the public in more detail how its scientific committees arrive at scientific conclusions, and how differences in views that arise during the assessment are addressed. This could be done, for example, by publishing more information online.

That the Agency considers making publicly available lists of all relevant documents in its possession related to a specific referral procedure, or that EMA consider other ways of helping citizens to identify the documents they wish to obtain.

Please find enclosed my decision on your complaint.



As I informed you in my letter of 8 November 2016, I decided to register your complaint under two case numbers (1475/2016/JAS dealing with the referral procedure, and 1606/2016/JAS dealing with the alleged conflict of interest involving a senior EMA staff member).

I have now concluded my analysis in the latter case. My conclusion, based on the evidence obtained by my inquiry team in a detailed inquiry, is that there are no interests that should have been declared, and therefore there was no maladministration by EMA. I will provide EMA and the complainants with a copy of my decision in that case as soon as it is available.

Yours sincerely,

Emily O'Reilly
European Ombudsman

Enclosure:

- Decision on complaint 1475/2017/JAS



European Ombudsman

Emily O'Reilly
European Ombudsman

Decision

in case 1475/2016/JAS on the European Medicines Agency's handling of the referral procedure relating to human papillomavirus (HPV) vaccines



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List of abbreviations

| | |
|-------|--|
| CHMP | Committee for Medicinal Products for Human Use |
| CRPS | Complex regional pain syndrome |
| EMA | European Medicines Agency |
| GACVS | Global Advisory Committee on Vaccine Safety |
| HPV | Human papillomavirus |
| MAH | Marketing Authorisation Holders |
| O/E | "Observed versus expected" |
| POTS | Postural orthostatic tachycardia syndrome |
| PRAC | Pharmacovigilance Risk Assessment Committee |
| SAG-V | Scientific advisory group on vaccines |
| WHO | World Health Organisation |



Abstract

This case concerned how the European Medicines Agency (EMA) carried out a “referral procedure”, which is a procedure to deal with questions relating to medicines already on the market in the EU. The specific referral procedure related to human papillomavirus (HPV) vaccines. HPV vaccines prevent infections with the most common types of HPV, which can cause cervical cancer.

The procedure was conducted by the Pharmacovigilance Risk Assessment Committee (PRAC), which is EMA’s committee responsible for monitoring the safety of medicines on the market. The aim of the procedure was to examine whether there is any evidence of a causal link between HPV vaccination and two syndromes, complex regional pain syndrome (CRPS), a chronic pain condition affecting the limbs, and postural orthostatic tachycardia syndrome (POTS), a condition where the heart rate increases after sitting or standing up, causing symptoms such as dizziness and fainting. PRAC concluded that the evidence did not support a finding that HPV vaccines cause CRPS or POTS. This finding was later confirmed by EMA’s Committee for Medicinal Products for Human Use. The finding is shared by other public health bodies around the world.

The complainants expressed concerns about the handling of the referral procedure, its transparency and openness, and its impartiality. They mainly disagreed with the nature of PRAC’s scientific work.

The European Ombudsman’s Office is not a scientific body. The Ombudsman’s role does not include taking a view on the merits of scientific evaluations carried out by specialised scientific agencies, such as EMA’s assessment of the safety of a medicine.

*The Ombudsman may, however, seek to assess whether scientific bodies such as EMA have the necessary procedural safeguards in place to ensure that the examination of scientific evidence is **complete and independent**, and whether these safeguards have been properly applied in any given procedure.*

Following her inquiry into the procedural aspects complained about, the Ombudsman concludes that her inquiry did not identify any procedural issues that could have negatively affected the work and conclusions of PRAC in the referral procedure. The examination of the scientific evidence was complete and it was independent.

Given the importance of ensuring citizens’ trust in the procedures of bodies such as EMA, the Ombudsman suggests that EMA proactively makes public as much information as possible on the scientific work of its committees.

In response to a suggestion made by the Ombudsman during her inquiry, EMA agreed to review the confidentiality requirements on experts so that experts may discuss in public details of the scientific debate once that debate has been completed.

The Ombudsman also suggests that EMA provides more information on the documents of relevance it has in its possession, so that it is easier for citizens to request access to such documents.

Finally, the Ombudsman considers that EMA’s conflict of interest policy was fully complied with during the referral procedure on HPV vaccines. There were no identified conflicts of interest. The procedure in question was therefore deemed to have been conducted in full independence by the relevant scientific experts.

The Ombudsman concludes that there was no maladministration by EMA in the handling of the referral procedure on HPV vaccines.



Background to the complaint

1. The complaint, submitted by three researchers, a medical doctor, and a Member of the European Parliament, concerns the European Medical Agency's handling of the so-called referral procedure on **human papillomavirus (HPV) vaccines**¹.
2. HPV vaccines prevent infections with the most common types of HPV, which can cause, in particular, **cervical cancer**. Cervical cancer is the fourth most common cancer in women worldwide, with about a quarter of a million deaths per year². In the European Union alone, every year 34,000 women are diagnosed with cervical cancers and 13,000 European women die annually of it³.
3. To date, data from clinical trials and post-marketing surveillance conducted on several continents have shown HPV vaccines to be safe⁴. Since the first authorisation of a HPV vaccine in 2006, over 270 million doses of HPV vaccines have been distributed worldwide. A 2017 review by the World Health Organisation's (WHO) Global Advisory Committee on Vaccine Safety⁵ (GACVS), which is a group of independent experts, identified no adverse reactions to the vaccines except for fainting, a common anxiety or stress-related reaction to the injection, and very rare cases (approximately 1.7 cases per million doses) of anaphylaxis (which is the technical name for a severe allergic reaction). Overall, GACVS considers HPV vaccines to be "*extremely safe*"⁶.
4. As the WHO considers HPV vaccines to be safe and effective, it recommends that HPV vaccines are included in national immunization programmes⁷. The EU Member States have followed that recommendation⁸. According to the GACVS, the benefits of these programmes are already apparent: Several countries that have introduced HPV vaccines have reported a 50% decrease in the rate of uterine cervix precancerous lesions among younger women. In contrast, the mortality rate from cervical cancer in other countries, where HPV vaccination is not proactively recommended, increased⁹.
5. In the EU, responsibility for the authorisation and safety supervision of HPV vaccines lies with the **European Medicines Agency (EMA)**. Within EMA, it is the **Pharmacovigilance Risk Assessment Committee (PRAC)**¹⁰ that is tasked with monitoring the safety of medicines already on the market. PRAC's members are national experts nominated by the EU Member States, as well as by Iceland and Norway. PRAC also includes independent scientific experts, as well as representatives from patient organisations and healthcare professions, all nominated by the European Commission¹¹.

¹ Marketed under the names *Cervarix*, *Gardasil*/*Silgard* and *Gardasil 9*.

² <http://gco.iarc.fr/today/fact-sheets-cancers?cancer=16&type=0&sex=2>

³ <http://eco.iarc.fr/eucan/CancerOne.aspx?Cancer=25&Gender=2#block-table-f>

⁴ <http://www.who.int/immunization/diseases/hpv/en/>

⁵ http://www.who.int/vaccine_safety/committee/en/

⁶ http://www.who.int/vaccine_safety/committee/topics/hpv/June_2017/en/

⁷ <http://apps.who.int/iris/bitstream/10665/255353/1/WER9219.pdf?ua=1>

⁸ <http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx>

⁹ http://www.who.int/vaccine_safety/committee/topics/hpv/June_2017/en/

¹⁰ http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000537.jsp

¹¹

http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/PRAC/people_listing_000112.jsp&mid=WC0b01ac058058f328



The names of all PRAC members are made public by EMA. The declarations of interests of all PRAC members are also made public by EMA.

6. The EU has put in place a system that monitors the safety of medicines throughout their use in practice (activities in this area are referred to as “**pharmacovigilance**”¹²). A crucial part of these efforts consists of managing and analysing information on suspected **adverse reactions** to medicines. In the EU, information on such reactions is collected in the EudraVigilance database¹³.

7. The rules governing EMA’s work include a number of so-called “**referral procedures**”, which are procedures used to ensure the safety or benefit-risk balance of a medicine after its authorisation¹⁴. During such a procedure, EMA’s scientific committees are tasked with conducting a scientific assessment on the issue raised. Referrals to EMA can be triggered by the Commission, any EU Member State or by the company that markets a medicine.

8. Concerning HPV vaccines, the referral procedure has been used to examine if there is any link between the vaccines and two syndromes, known as **complex regional pain syndrome (CRPS)**, a chronic pain condition affecting the limbs) and **postural orthostatic tachycardia syndrome (POTS)**, a condition where the heart rate increases after sitting or standing up, causing symptoms such as dizziness and fainting, as well as headache, chest pain and weakness). Both syndromes occur in the general population regardless of vaccination, and may overlap with other conditions, making diagnosis difficult both in the general population and vaccinated individuals¹⁵. The referral procedure was launched in July 2015 by the Commission at the request of Denmark¹⁶. The Commission asked EMA to give its opinion on whether there was any evidence of a causal link between HPV vaccination and CRPS and/or POTS and, if so, whether changes to product information were necessary¹⁷.

9. Following the launch of the referral procedure, PRAC nominated the UK PRAC member as the PRAC **rapporteur**. PRAC also nominated the Swedish PRAC member and the Belgian PRAC member as **co-rapporteurs**¹⁸. These three PRAC members took the lead in the scientific assessment. PRAC also prepared a list of questions to be answered by the companies marketing the vaccines (which are referred to as Marketing Authorisation

¹²

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000258.jsp&mid=WC0b01ac0580b18c76

¹³ Certain data from EudraVigilance is publicly available at: <http://www.adrreports.eu/en/index.html>

¹⁴ http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp

¹⁵

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Human_papillomavirus_vaccines/human_referral_prac_000053.jsp&mid=WC0b01ac05805c516f

¹⁶ In accordance with Article 20 of Regulation 726/2004 (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>.

¹⁷

http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/HPV_vaccines_20/Procedure_started/WC500189479.pdf

¹⁸ http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2015/09/WC500194105.pdf



Holders or MAHs). These questions were later published¹⁹. The MAHs' responses were then shared with every PRAC member, together with the (co-)rapporteurs' assessment of the responses and of other available data, for example from EudraVigilance.

10. During its evaluation, PRAC also consulted the **scientific advisory group on vaccines (SAG-V)**²⁰, composed of independent experts on vaccines, which provided advice to PRAC on a number of questions. The SAG-V meeting in which HPV vaccines were discussed also included experts on the syndromes under investigation, on neurology, cardiology and pharmacoepidemiology. The SAG-V's advice to PRAC was later made public as part of the final assessment report²¹.

11. In November 2015, PRAC concluded that the **evidence did not support a finding that HPV vaccines cause CRPS or POTS**. The review found **no evidence** that the overall rates of these syndromes in vaccinated girls were different from expected rates of these syndromes in these age groups, even taking into account possible underreporting. PRAC therefore considered that there was no reason to change the way the vaccines were used or to amend the current product information. PRAC also stated that the benefits of HPV vaccines continued to outweigh any risks. PRAC's 40-page assessment report was subsequently made publicly available²².

12. PRAC's conclusions are shared by other public bodies. In 2017, WHO's GACVS reaffirmed its 2016 finding²³ that there was no evidence to suggest a causal link between HPV vaccine and CRPS or POTS²⁴. In the United States, monitoring by the Centers for Disease Control and Prevention has not detected any safety concerns related to CRPS or POTS following HPV vaccination²⁵.

13. EMA's **Committee for Medicinal Products for Human Use (CHMP)**²⁶, the committee responsible for human medicines made of up of high level experts appointed by every EU Member State²⁷, unanimously agreed with PRAC's recommendation. The CHMP, as a

¹⁹

http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/HPV_vaccines_20/Procedure_started/WC500189477.pdf

²⁰

http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/CHMP/people_listing_000116.jsp&mid=WC0b01ac058058f32e

²¹ Pages 32-36 of the final assessment report, 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

²²

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

²³ <http://www.who.int/wer/2016/wer9103.pdf?ua=1>

²⁴ http://www.who.int/vaccine_safety/committee/topics/hpv/June_2017/en/

²⁵ <https://www.cdc.gov/vaccinesafety/vaccines/hpv/hpv-safety-faqs.html>

²⁶ The CHMP is responsible for: conducting the initial assessment of EU-wide marketing authorisation applications; assessing modifications or extensions to an existing marketing authorisation; and considering the recommendations of the PRAC on the safety of medicines on the market

http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000094.jsp.

²⁷

http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/2010/02/people_listing_000002.jsp&mid=WC0b01ac0580028c7c



consequence, concluded that the benefit-risk balance of HPV vaccines remained favourable and recommended the maintenance of the marketing authorisations²⁸.

14. In January 2016, the Commission issued decisions maintaining the marketing authorisations for HPV vaccines²⁹.

15. In May 2016, the complainants contacted EMA regarding the handling of this referral procedure. They also asked EMA for related documents. EMA replied to the complainants and granted them access to the documents requested (minutes of the SAG-V meeting).

16. The complainants submitted a complaint to the Ombudsman in October 2016.

The inquiry

17. The Ombudsman opened an inquiry into the complaint. The complainants' position is that:

- 1) EMA's PRAC committed errors during its handling of the referral procedure;
- 2) The referral procedure was not sufficiently transparent and open;
- 3) The handling of conflict of interest issues related to the referral procedure was inadequate.

18. The Ombudsman first met with EMA to clarify the complainants' concerns. The Ombudsman then asked EMA to reply to a number of questions based on the complainants' arguments. The Ombudsman also received the comments of the complainants on EMA's reply. Finally, the Ombudsman asked EMA to give her the unredacted versions of all internal reports produced during the referral procedure. The Ombudsman's decision takes all of the above into account plus the extensive documentation made available.

The Ombudsman's assessment of the referral procedure on HPV vaccines

19. The complaint and its analysis is necessarily detailed and complex. This decision therefore gives an overview of the main findings while a detailed assessment of the complainants' arguments is in the **annex**.

²⁸

[http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/HPV_vaccines_20/European Commission_final_decision/WC500200002.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/HPV_vaccines_20/European_Commission_final_decision/WC500200002.pdf)

²⁹ Available at: http://ec.europa.eu/health/documents/community-register/2016/20160112133731/dec_133731_en.pdf (Cervarix), http://ec.europa.eu/health/documents/community-register/2016/20160112133737/dec_133737_en.pdf (Gardasil),

http://ec.europa.eu/health/documents/community-register/2016/20160112133733/dec_133733_en.pdf (Gardasil 9) and http://ec.europa.eu/health/documents/community-register/2016/20160112133739/dec_133739_en.pdf (Silgard).



On PRAC's assessment

20. The complainant put forward a number of concerns regarding the referral procedure on HPV vaccines. In the referral procedure, PRAC was asked to conduct a scientific assessment, namely to assess whether there was any evidence of a causal association between HPV vaccination and the syndromes CRPS and POTS³⁰.
21. The Office of the European Ombudsman is not a scientific body. The Ombudsman deals with complaints about *administrative* activities and it is not within her mandate³¹ to examine the merits of scientific evaluations carried out by specialised scientific agencies.
22. However, the Ombudsman may seek to assess whether scientific bodies such as EMA have the **necessary procedural safeguards in place** to ensure that the scientific advice they receive is as complete as possible and independent, and **whether these safeguards have been properly applied in any given procedure**³².
23. In terms of the procedure, the Ombudsman notes that the members of PRAC took their decision on the referral procedure on the basis of extensive data. That data was provided by the companies that market HPV vaccines but also from other sources, including EMA's own database on adverse reactions, Member States, and from submissions by patient groups. The (co-)rapporteurs, the PRAC members who took the lead in the scientific assessment, evaluated all that data, which was then shared with all members of PRAC. All PRAC members then had the opportunity to comment on all the available data and the conclusions drawn by the (co-)rapporteurs. Any comments that PRAC's members had were addressed by the (co-)rapporteurs.
24. PRAC's members did put forward different views at the beginning of the procedure. However, following the evaluation of all the evidence, and following the exchanges of views in PRAC and consultation with a group of independent experts, **every member of PRAC stated that the vaccines do not cause the two syndromes under investigation, CRPS and POTS**.
25. Since every member of PRAC agreed with the conclusion that the vaccines do not cause the two syndromes under investigation, the Ombudsman must therefore take the view that each PRAC member considered that any initial concerns had been adequately addressed. PRAC's findings were then approved by the CHMP, EMA's highest-ranking committee for human medicines. As a precautionary measure, and consistent with its practice across many medicines, PRAC recommended that the safety of HPV vaccines should continue to be carefully monitored.

³⁰

http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/HPV_vaccines_20/Procedure_started/W/C500189479.pdf

³¹ Article 228(1) TFEU: "A European Ombudsman, elected by the European Parliament, shall be empowered to receive complaints from any citizen of the Union or any natural or legal person residing or having its registered office in a Member State **concerning instances of maladministration** in the activities of the Union institutions, bodies, offices or agencies, with the exception of the Court of Justice of the European Union acting in its judicial role. He or she shall examine such complaints and report on them" (emphasis added).

³² See Decision in case 1375/2016/JAS on the European Commission's handling of concerns regarding the renewal of the approval of the herbicide ingredient glyphosate, paragraph 18, available at: <https://www.ombudsman.europa.eu/en/cases/decision.faces/en/75832/html.bookmark>



26. The complainants mainly dispute PRAC's scientific work. They disagree with the scientific findings that PRAC made, which were based on the available data. They also question the scientific appropriateness of the methodology applied to identify that data. As already explained, the Ombudsman is not in a position to take a view on questions of science. She notes, however, that PRAC's expert members reached consensus on their conclusions. PRAC's view was confirmed by CHMP, again, a committee also made up of qualified experts.

27. In light of the above, the Ombudsman finds no maladministration in relation to the way in which PRAC carried out its work.

28. The Ombudsman acknowledges the inherent difficulties in communicating a highly complex scientific procedure such as the referral of a medicine. She therefore suggests that EMA finds ways to explain in more detail—for example by publishing more information online—how its scientific committees arrive at conclusions, and how differences in views that arise during the assessment are addressed.

On transparency and openness

29. The complainants argued that the confidentiality that EMA requires from its scientific experts is too restrictive. The Ombudsman agrees that transparency around such discussions builds trust in EMA and EMA's work.

30. The Ombudsman therefore suggested that EMA might improve the situation. EMA has now agreed to review its standard confidentiality declarations so that experts may, under certain conditions, discuss in public the debate that has occurred in scientific committees such as PRAC once a matter has been concluded.

31. The Ombudsman also suggested to EMA that it consider making publicly available lists of all its relevant documents on specific referral procedures. This would make it easier for citizens to identify relevant documents and reduce the administrative burden on EMA. Alternatively, EMA might consider other ways of assisting citizens in identifying such documents.

32. Finally, the Ombudsman considers that EMA's decision to redact the names of some of its staff from documents requested by the complainants was in line with the EU rules on data protection³³.

On alleged conflicts of interest

33. The complainants raised a number of concerns regarding EMA's conflict of interest practices concerning its scientific experts, such as those involved in the referral procedure on HPV vaccines.

³³ 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 institutions and bodies of the Community and on the free movement of such data, OJ 2001 L 8, p. 1, available at: <http://data.europa.eu/eli/reg/2001/45/oj>



34. EMA's scientific experts are subject to EMA's policy on the handling of competing interests of scientific committees' members and experts³⁴. As part of this, EMA maintains a public database on all experts who serve as members in EMA's scientific committees, working parties and other groups, or that otherwise provide scientific expertise³⁵. This database contains the experts' declarations of interest. Every year, the experts sign the declaration so that EMA can check that they do not have any financial or other interests in the pharmaceutical industry that could affect their impartiality.

35. One of the complainants' concerns was that they could not find, in the database, the declarations of two of the experts who had been involved in the referral procedure on HPV vaccines.

36. The Ombudsman asked EMA to provide the missing declarations, which it did. These declarations did not show any interests which might have compromised their independence and their participation in the procedure was therefore deemed to be legitimate. EMA explained that these declarations had not been in its database because their old declarations had expired, and had been automatically removed from the database when the complainants tried to access them. The Ombudsman notes that regularly renewing interest declarations constitutes good administrative practice.

37. The complainants also raised concerns about the participation of certain experts in the SAG-V, the expert group that advised provide PRAC. Having obtained and examined the declarations of interest of all the experts in question, the Ombudsman concludes that the decisions regarding participation of experts in the SAG-V were reasonable and in line with EMA's conflict of interest policy.

Conclusion

Based on the inquiry, the Ombudsman closes this case with the following conclusion³⁶:

There was no maladministration by the European Medicines Agency in the handling of the referral procedure on HPV vaccines.

The complainants and EMA will be informed of this decision.

Suggestions for improvement

The Ombudsman suggests that the European Medicines Agency continue to explore ways to explain to the public in more detail how its scientific committees arrive at scientific conclusions, and how differences in views that arise during the assessment are addressed. This could be done, for example, by publishing more information online.

³⁴ Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/11/WC500216190.pdf

³⁵ http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/landing/experts.jsp

³⁶ Information on the review procedure can be found on the Ombudsman's website: <http://www.ombudsman.europa.eu/en/resources/otherdocument.faces/en/70669/html.bookmark>



The Ombudsman suggests that the European Medicines Agency consider making publicly available lists of all relevant documents in its possession related to a specific referral procedure, or that EMA consider other ways of helping citizens to identify the documents they wish to obtain.

Emily O'Reilly
European Ombudsman

Strasbourg, 16/10/2017



Annex - Detailed assessment of the complainants' arguments

a. On PRAC's assessment

Overview of the referral procedure

1. EMA's referral procedure on HPV vaccines consisted of the following steps³⁷:

| Date | Procedural steps |
|---------------------|---|
| July 2015 | The European Commission triggers the referral procedure on HPV vaccines ³⁸ |
| 6-9 July 2015 | EMA's Pharmacovigilance Risk Assessment Committee (PRAC) launches its procedure, appoints (co-)rapporteurs and adopts list of questions ³⁹ to be answered by the companies selling the HPV vaccines (these companies are known as Marketing Authorisation Holders or MAHs) ⁴⁰ |
| August 2015 | The MAHs submit their replies to PRAC |
| 25 September 2015 | The preliminary assessment reports of the rapporteur and the two co-rapporteurs are circulated to PRAC and EMA's Committee for Medicinal Products for Human Use (CHMP) |
| 5-8 October 2015 | PRAC adopts list of questions for the Scientific Advisory Group on Vaccines (SAG-V) experts ⁴¹ |
| 21 October 2015 | Meeting of the SAG-V |
| 28 October 2015 | Updated (co-)rapporteurs preliminary assessment reports are circulated to PRAC and the CHMP |
| 3-6 November 2015 | PRAC adopts, by consensus, its conclusion that the available evidence does not support a finding that HPV vaccines cause CRPS and POTS and recommends the maintenance of the marketing authorisations ⁴² . |
| 16-19 November 2015 | The CHMP agrees with PRAC's findings and adopts an opinion by consensus recommending that the marketing authorisations for HPV vaccines should be maintained ⁴³ . |

³⁷ See also "Timetable for the procedure", available at:

http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/HPV_vaccines_20/Procedure_started/WC500189478.pdf

³⁸

http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/HPV_vaccines_20/Procedure_started/WC500189479.pdf

³⁹

http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/HPV_vaccines_20/Procedure_started/WC500189477.pdf

⁴⁰ http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2015/09/WC500194105.pdf

⁴¹ http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2015/11/WC500197320.pdf

⁴² http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2016/01/WC500199609.pdf

⁴³ http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2015/12/WC500199231.pdf



The preliminary assessment reports

2. As can be seen in the above table, the rapporteur (the UK PRAC member) and the two co-rapporteurs (the Swedish PRAC member and the Belgian PRAC member) produced two rounds of preliminary assessment reports at different stages of the referral procedure on HPV vaccines. The complainants argued that divergent opinions expressed by the PRAC co-rapporteurs in these reports were left out of PRAC's final, publicly available assessment report⁴⁴.

3. In the first preliminary assessment reports of September 2015, the co-rapporteurs and the rapporteur, each responsible for different HPV vaccines and the latter also responsible for the overall assessment, mainly analysed and assessed in detail the replies by the Marketing Authorisation Holders (MAHs) to the questions posed by PRAC. The rapporteur's report also contains a summary of the co-rapporteurs' reports as well as an assessment of the co-rapporteurs' preliminary conclusions. All three preliminary assessment reports were then made available to all PRAC members, who were invited to comment.

4. EMA stated that the opinions set out in the preliminary assessment reports constituted "work in progress" and that these opinions could, and did, change as a result of the deliberations and discussions amongst the PRAC members. According to EMA, 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 stated that preliminary conclusions of the (co-)rapporteurs *"in no way bind the PRAC to its final conclusions, which take into account the views expressed by all PRAC members, the uncertainties identified during the procedure and responses to scientific questions posed by the PRAC"*. In this case, for example, one of the co-rapporteur had reconsidered certain views following comments from Member States and the input of the SAG-V experts.

5. EMA said that any PRAC member (including any co-rapporteur) who continues to have reservations at the end of the procedure may raise those concerns by voting against the committee majority and expressing a divergent position. The reasons for any divergent positions are then made available to the public as part of the documentation on the outcome of the procedure⁴⁵.

6. The Ombudsman notes that all members of PRAC were provided with the (co-) rapporteurs' preliminary assessment reports and had the opportunity to comment on, and to discuss, any views expressed therein. However, even if certain members expressed divergent opinions **during** the course of the procedure, they obviously considered their opinions to have been properly addressed **by the end of the procedure**. This is evidenced by the fact that **all PRAC members, including both co-rapporteurs, agreed with the final**

⁴⁴ 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

⁴⁵ See, for example, Assessment report cyproterone acetate/ethinylestradiol (2 mg/0.035 mg) containing medicinal products, pages 38-39, available at:

http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/cyproterone_ethinylestradiol_107i/Recommendation_provided_by_Pharmacovigilance_Risk_Assessment_Committee/WC500144130.pdf



recommendation adopted by PRAC⁴⁶. Contrary to the complainants' claims, none of the co-rapporteurs, nor any other PRAC member, was "overruled" by PRAC.

Publication of the preliminary assessment reports

7. The complainants argued that the final, publicly available assessment report did not reflect the opinions expressed by the co-rapporteurs in their preliminary assessment reports. These reports, which can undergo several modifications during a procedure, are not made proactively publicly available.

8. The Ombudsman asked EMA to consider making available more information on its assessments, including on how any divergent views expressed during the process are addressed.

9. EMA replied that differences in opinion are made publicly available as an annex to the final report if those differences persist until the adoption of the final report (for an example, see footnote 45). However, if such preliminary views are not maintained at the end of the procedure, the publication of such information could give rise to confusion as to the final conclusions reached.

10. Nevertheless, EMA stated, any request for public access to documents containing preliminary views, such as the preliminary assessment reports of the (co-)rapporteurs, are processed in accordance with the rules on access to documents⁴⁷. Thus, anybody interested in the preliminary work leading up to the final recommendations can submit a request for public access to those documents. Regarding the referral procedure on HPV vaccines, for example, the preliminary assessment report of one of the co-rapporteurs was released following such a request (with only limited redaction of data, for example the personal data of patients).

11. The Ombudsman finds EMA's explanations on this point generally to be reasonable. It is important for EMA to focus public attention on the agreed findings of its scientific committees. If one or more experts disagree with these findings, their views should, as is practice, be made public. However, all members of PRAC agreed with the final assessment report on HPV vaccines, and there were thus no differences of opinion at the end of the procedure.

12. Nevertheless, the Ombudsman is aware that the work of EMA's scientific committees is highly complex and potentially difficult to communicate to interested citizens. **While the Ombudsman welcomes EMA's efforts in explaining this work⁴⁸, she suggests that EMA continue to explore ways to explain in even more detail, for example by publishing more information online, how its scientific committees work to arrive at**

⁴⁶ See page 14 of the minutes on PRAC's November 2015 plenary, available at:

http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2016/01/WC500199609.pdf

⁴⁷ More information on EMA's access to documents regime is available at:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/document_library/document_listing/document_listing_000312.jsp&

⁴⁸ See, for example:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_001787.jsp&mid=WC0b01ac0580b2c7ee



scientific conclusions, and how differences in views that arise during the assessment are addressed.

The “updated assessment report”

13. The complainants asked EMA to explain a number of statements made in one of the preliminary assessment reports. This report, which is the one that was made publicly available following an access to documents request, was produced by one of the co-rapporteurs and is an update of that co-rapporteur’s report of 25 September 2015. The complainants argued that statements in this report show that criticisms made by that co-rapporteur were, later on, simply discarded by PRAC.

14. In order to assess the complainants’ argument, the Ombudsman asked EMA to provide her with **unredacted versions of all preliminary assessment reports produced during the referral procedure on HPV vaccines**. As outlined in the overview above, all three (co-)rapporteurs updated their preliminary assessment reports at the end of October 2015, taking into account additional information gathered since the first version. Among other things, these updated reports contain comments received from other PRAC members and the (co-)rapporteurs’ assessment of these comments.

15. The Ombudsman notes that the statements referred to by the complainants were in fact comments made by a Member State PRAC member and not comments by the co-rapporteur. The complainants appear to mistake these statements as (allegedly discarded) criticisms made by the co-rapporteur.

16. The preliminary report in question shows that the comments made by this Member State PRAC member were assessed by the co-rapporteur and the co-rapporteur explains how these comments are addressed. Similarly, the updated preliminary assessment reports of the rapporteur and the other co-rapporteur also contain analyses of the comments received from Member States.

17. The Ombudsman sees nothing untoward in this process, which reflects the normal course of scientific discourse, where questions are put forward and then addressed. Indeed, the fact that there is open, detailed and robust exchange of views within PRAC is reassuring. Furthermore, it must have been the case that all Member State members on PRAC felt that their comments had been addressed and taken into account properly, as there was consensus among all the members on PRAC’s final recommendations.

Consensus-based decision-making

18. The complainants suggest that scientific committees that aim to reach decisions by consensus, such as PRAC, 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.

19. The Ombudsman notes that **striving** for scientific consensus in PRAC is expressly provided for by law⁴⁹.

⁴⁹ 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



20. Furthermore, scientific bodies at the WHO⁵⁰ and in the United States⁵¹ equally use consensus-based decision-making. The complainants claim that, in such a system, people are not likely to express disagreement with the majority. The Ombudsman disagrees. The duty to **strive** for consensus, using best endeavours, does not mean that a consensus must be found. It is legally possible for PRAC to arrive at a position without reaching a consensus since the law states that “*If such a consensus cannot be reached, the opinion [of PRAC] shall consist of the position of the majority of members and divergent positions, with the grounds on which they are based*”⁵². Indeed, there are examples of PRAC reaching decisions by majority and not by consensus⁵³. Thus, the Ombudsman concludes that where PRAC does decide to adopt a decision by consensus, without any divergent views being expressed, as it did as regards the HPV vaccines, it is because the members of PRAC, after discussion and deliberation amongst each other, reached a common view on the issues before them.

21. The complainants also claim that members of the SAG-V, which was asked by PRAC for input on a number of questions, were pressured into adopting a certain point of view.

22. The Ombudsman has seen no evidence of any pressure being exerted on any member of the SAG-V. The Ombudsman also notes that, similar to the PRAC, the members of SAG-V are not required to reach a consensus. The SAG-V can adopt a position on the basis of a majority vote if no consensus can be reached⁵⁴. Therefore, the Ombudsman concludes that if any members of SAG-V were minded to give a view which differed from the views of his or her colleagues, they were free to do so.

Information provided by the producers of the vaccines

23. The complainants also questioned the methodology applied by PRAC. They argued that the information provided by the producers of the vaccines (the MAHs) was not scrutinised and independently assessed by PRAC. According to the complainants, PRAC simply accepted the data received from the MAHs at face value.

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

opinion shall consist of the position of the majority of members and divergent positions, with the grounds on which they are based.”

⁵⁰ Decisions or recommendations of the GACVS are, as a rule, taken by consensus (http://www.who.int/vaccine_safety/committee/working_mechanisms/en/). The WHO's International Agency for Research on Cancer (IARC) Monograph Working Groups strive to achieve a consensus evaluation (<http://monographs.iarc.fr/ENG/Preamble/currenta6work0706.php>).

⁵¹ The Food and Drug Administration's Drug Safety Oversight Board formulates its recommendations through consensus or by vote (<https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM073564.pdf>).

⁵² Article 61(7) of Regulation 726/2004.

⁵³ See, for example, page 10 of the minutes of the 13-16 May 2013 PRAC meeting (http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2013/06/WC500144716.pdf) and assessment report cyproterone acetate/ethinylestradiol (2 mg/0.035 mg) containing medicinal products, pages 38-39, (available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/cyproterone_ethinylestradiol_107i/Recommendation_provided_by_Pharmacovigilance_Risk_Assessment_Committee/WC500144130.pdf). In that case, the views of the PRAC member expressing a dissenting view from the majority were set out in detail in the PRAC assessment report.

⁵⁴ http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/06/WC500091622.pdf



25. EMA explained that the MAHs were legally obliged to provide, to the regulatory authorities, **all available data** they had in their possession and that there were mechanisms in place to ensure that this was abided by. EMA also confirmed that, in line with standard practice, **all documentation** submitted in the context of the referral procedure, including from MAHs, was made available to all PRAC members, mainly through a dedicated electronic portal available on the EMA website⁵⁵.

26. The Ombudsman also notes that the preliminary assessment reports of the rapporteur and co-rapporteurs do in fact contain a detailed assessment of the information provided by the MAHs. Among other things, the (co-)rapporteurs assessed the methodology applied by the MAHs when they collected information. The rapporteur also reviewed the co-rapporteurs' assessments. As outlined above, the data and the (co-)rapporteurs' assessments were then provided to **all** PRAC members, who could submit comments thereon if they so wished – which some of them did. It is thus not correct that the data provided by the MAHs was accepted “at face value”. Rather, it was rigorously examined.

27. It is also clear from the available documentation that PRAC did not rely solely on information provided by the MAHs. During the assessment, the (co-)rapporteurs also took into account the input of the SAG-V experts⁵⁶, comments provided by Member States, the results of literature searches conducted by EMA, data extracted by EMA from its EudraVigilance database on adverse reactions⁵⁷, additional scientific studies⁵⁸ and submissions by doctors and patient groups⁵⁹. In particular, PRAC assessed at length a report submitted by Denmark, the Member State that asked the Commission to trigger the referral procedure⁶⁰. The Ombudsman thus considers that PRAC took due account of **all** available information.

28. All PRAC members clearly considered that the information obtained from all the above sources was sufficiently extensive and detailed to allow them to reach a view on the issues before it. In support of this conclusion, the Ombudsman notes that PRAC was entitled to request additional data from whatever source. It did not consider it necessary to do so. In addition, the Ombudsman notes that members of PRAC could have voted against the final recommendations, if they considered the available data to be insufficient to back up PRAC's scientific conclusions. However, all members of PRAC supported the final recommendations.

29. Inasmuch the complainants disagree with the scientific conclusions based on the data obtained, or the scientific appropriateness of the methodology applied to identify relevant data, the Ombudsman notes that it is not for the Ombudsman to take a position on issues of science.

Analyses of adverse events

30. The complainants argued that certain cases of suspected POTS, identified in the company safety database, were “overruled” by one of the MAHs and judged as not

⁵⁵ <http://esubmission.ema.europa.eu/>

⁵⁶ See pages 32-36 of the final assessment report.

⁵⁷ See page 31 of the final assessment report.

⁵⁸ See page 30-31 of the final assessment report.

⁵⁹ See also page 32 of the final assessment report.

⁶⁰ The final assessment report includes, on pages 21-30, a detailed summary and analysis of the contents of this report.



meeting, or only partially meeting, the diagnostic criteria for the syndrome. The complainants questioned how the MAH was able to dismiss a diagnosis without having access to the medical reports or to the patients.

31. The Ombudsman notes that the submission to PRAC by the MAH in question included summary analyses of **every identified case**, that is, **also** of those cases that the MAH considered did not meet the criteria for POTS. This summary included, among other things, the case number, the MAH's assessment of whether the different criteria of the syndrome were met and the MAH's comments on each individual case. Furthermore, EMA stated that the narratives of all reported cases were included by the MAH in the relevant documentation and thus were made available to the (co-)rapporteurs and all other PRAC members.

32. The Ombudsman notes that the (co-)rapporteurs' preliminary assessment reports show that the (co-)rapporteurs assessed and agreed both with the case detection *methods* and the *classification* of cases as fulfilling the criteria for POTS, partially fulfilling them or not being POTS. This assessment was then shared with all PRAC members.

33. The preliminary assessment reports also show that the approach to cases considered not to meet the criteria was discussed among the PRAC members following comments by a Member State. Ultimately, PRAC concluded in its final assessment report concerning this MAH: *"It is noted that the MAH did not include a conservative analysis to include all cases of POTS, including those that do not meet the diagnostic criteria, however, it is considered that this approach would not add value and would simply have included cases that are unlikely to be POTS. Furthermore, the number of expected cases would not have been as relevant in such analyses"*⁶¹.

34. PRAC thus clearly considered both the approach to these cases as well as whether to include them in its analysis, but decided against it on scientific grounds. Consensus on the final report again shows that **all PRAC members** were satisfied with this approach. The Ombudsman cannot question that scientific judgment.

Search strategies for undiagnosed adverse events

35. The complainants expressed their disagreement with the search strategies used by the MAHs to identify possible cases of undiagnosed CRPS and POTS based on a search for various combinations of symptoms for each syndrome.

36. In their reply to the PRAC, the MAHs were required to explain the algorithms used to identify such cases by searching for combinations of signs and symptoms common in CRPS or POTS⁶². The algorithms were then reviewed in the preliminary assessment reports of the rapporteur and the co-rapporteurs, and shared with all PRAC members. No objections were raised.

⁶¹ Page 17 of the final assessment report.

⁶² See question 1 of the list of questions, available at:

http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/HPV_vaccines_20/Procedure_started/WC500189477.pdf



37. While the Ombudsman cannot take a view on whether the search terms used by the MAHs are scientifically appropriate, she notes that the PRAC's members were fully aware of how the MAHs were using search terms and no PRAC member expressed any view that the search terms were inappropriate.

"Observed vs expected analysis"

38. The complainants also criticised PRAC's use of a so-called "observed versus expected" (O/E) analysis. For this analysis, the number of adverse reactions identified as meeting or partially meeting the criteria of the syndromes under investigation were compared with the number of cases that would be expected to have occurred naturally in the target population⁶³. The complainants argued that analyses based on "expected incidence" were unreliable.

39. The Ombudsman notes that the available documentation shows that PRAC was fully aware of the technical limitations of the available data, a fact that was expressly discussed by the (co-)rapporteurs in their respective preliminary assessment reports and commented upon by other Member States. According to PRAC's final report, *"Observed versus expected (O/E) analyses cannot determine causality, but they are useful in signal validation [that is, the process of evaluating data that might suggest a possible causal association between a medicine and an adverse reaction] and, in the absence of robust epidemiological data, in preliminary signal evaluation"*⁶⁴.

40. PRAC also explained the measures taken to address these limitations: *"Given uncertainties around the 'observed' number of cases, the levels of diagnostic certainty, the level of vaccine exposure and the background incidence rates, sensitivity analyses are usually applied in statistical analyses around assumed levels of under-reporting, numbers of 'confirmed' and 'non-confirmed' cases (using several categories of diagnostic certainty as appropriate), numbers of vaccinated individuals or vaccine doses administered and confidence intervals of incidence rates"*⁶⁵ (emphasis added).

41. For example, to take account of possible underreporting, the O/E analysis included scenarios which assumed a reporting rate of cases **as low as 1%** (meaning that, in this scenario, it is assumed, for the purposes of statistical analysis, that the cases identified represent only a hundredth of the actual number of cases)⁶⁶.

42. PRAC also asked the SAG-V experts to comment on the available information. The experts responded that *"The O/E analysis conducted by the MAHs in the frame of the referral, and thoroughly assessed by the Rapporteurs, seems to be as robust as it could be, given the difficulties with the type of data gathered and the assumptions made. [...] [I]t was noted that the O/E analyses covered a range of scenarios [...] and the most plausible scenarios showed no excess of POTS or CRPS cases above the background rate considering the situation in individual countries [...]"*⁶⁷.

⁶³ See also pages 12-13 of the final assessment report.

⁶⁴ Page 13 of the final assessment report.

⁶⁵ Page 13 of the final assessment report.

⁶⁶ See, for example, page 16 of the final assessment report.

⁶⁷ Pages 34-35 of the final assessment report.



43. Ultimately, PRAC stated, **in full cognisance and consideration of the limitations of such analyses**, that, in the O/E analyses, the rates of CRPS/POTS in vaccinated girls were consistent with expected rates in these age groups, taking into account a wide range of scenarios regarding underreporting as well as reports that did not fully meet the diagnostic criteria for the syndromes⁶⁸. The Ombudsman takes no view on the scientific aspects of this question, but notes that PRAC was fully aware and open about the limitations of the O/E analysis and explained the measures taken to address these limitations. Ultimately, all experts agreed on the conclusions drawn from the available data.

Pooling of placebos

44. The complainants also did not agree with the methodology applied to compare the number of possible cases of CRPS and POTS among the group that received, during clinical trials, HPV vaccines with the group that received placebos. The MAHs had pooled together results of multiple completed studies, which had used different types of placebos. The complainants argue that the choice of at least some of these placebos may have been problematic.

45. EMA explained that the pooling was considered appropriate, despite the different placebos, as the data was used **only** to gather information on the **overall** number of cases of POTS and CRPS for the purpose of detecting the potential existence of a safety “signal” linked to HPV vaccines. In fact, the number of suspected cases of CRPS/POTS amongst the clinical trial data was so low that the pooling of placebo groups was not relevant for the scientific assessment. For one of the vaccines, no cases of CRPS or POTS were identified at all, neither in the group that received the HPV vaccine nor the one that received placebos⁶⁹. Regarding the other group of vaccines, only three reports suggestive of CRPS (one in *Gardasil 9*, one in *Gardasil/Silgard* and 1 in placebo) and two cases suggestive of POTS (two in *Gardasil 9* and none in *Gardasil/Silgard* or placebo) were identified among the about 60,000 trial participants. The (co-)rapporteurs analysed each of the identified suggestive cases, regardless of whether a case concerned the HPV vaccine group or the placebo group⁷⁰. That assessment was again shared with all PRAC members. Overall, PRAC noted that the incidence of both syndromes was very low, both in the vaccinated group as well as in the placebo groups.

46. The Ombudsman notes that contrary to what the complainants argue, PRAC did not *compare* the number of possible cases of CRPS and POTS among the group that received HPV vaccines with the group that received (different types of) placebos. The very low number of possible cases would not have allowed for any relevant comparison. PRAC therefore compared the number of possible cases identified in both groups with the estimated incidence of POTS and CRPS in the general unvaccinated population (see also paragraphs 38 to 43 regarding the O/E analysis). PRAC concluded that the low incidence of cases during clinical trials was, in fact, in line with the estimated incidence of such conditions in the general unvaccinated population.

⁶⁸ See page 39 of the final assessment report.

⁶⁹ Page 13 of the final assessment report.

⁷⁰ See also page 15 of the final assessment report.



47. The complainants also question the scientific appropriateness of the use of certain types of placebos during the clinical trials on HPV vaccines. The Ombudsman cannot take a view on this question of science.

Need for more research

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

49. In response, EMA provided explanations on its efforts to monitor and analyse pharmacovigilance data⁷¹. EMA also described the obligations imposed on the MAHs of HPV vaccines, as well as the recommendations made by PRAC following the referral procedure. Based on the EU pharmacovigilance legislation⁷², EMA obliges the MAHs to put in place risk management systems and to perform the activities outlined in risk management plans⁷³. Furthermore, PRAC recommended, in the final assessment report, that the “*safety of these vaccines should **continue to be carefully monitored**. This should include follow-up of CRPS or POTS reports to determine relevant clinical characteristics, to identify possible cases of POTS and CRPS based on broad search strategies including outcome details and to compare reporting rates against available information on the known epidemiology of POTS and CRPS*”⁷⁴ (emphasis added).

50. Furthermore, the CHMP, when issuing its opinion on the referral procedure, considered “*that ‘Observed versus expected’ analysis should continue to be performed in [periodic safety update reports, that is, the reports prepared by the MAH describing the safety experience with a medicine at defined times after its authorisation,] considering changes in reporting rates*”⁷⁵.

51. The publicly available information shows that PRAC considered whether additional studies should be requested from the MAHs. PRAC also asked SAG-V to discuss the feasibility of such studies⁷⁶. In the end, PRAC concluded that requesting such studies was not warranted⁷⁷.

52. The complainants did not agree with PRAC’s scientific conclusions and argued that EMA could and should have concluded that more research was needed. The Ombudsman cannot take a view on the conclusions drawn from the available data, but notes PRAC’s and EMA’s commitment to the ongoing monitoring of the safety of HPV vaccines.

⁷¹ See also

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001819.jsp&mid=WC0b01ac05800241de

⁷² Article 21(2) of Regulation 726/2004.

⁷³ See Annexes II to the European Public Assessment Report for *Cervarix*

(http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000721/WC500024632.pdf) and *Gardasil*

(http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000703/WC500021142.pdf).

⁷⁴ Page 39 of the final assessment report.

⁷⁵ http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2015/12/WC500199231.pdf

⁷⁶ Page 36 of the final assessment report.

⁷⁷ Page 37 of the final assessment report.



EMA's literature searches

53. The complainants argued that EMA had removed its literature searches on CRPS and POTS from one of the co-rapporteur's preliminary assessment report.

54. EMA stated that, in principle, literature searches are not confidential information and are therefore not redacted from a document released following a request for public access. However, EMA acknowledged that when it processed a request for access to the preliminary assessment report, the searches had been inadvertently deleted.

55. Following a subsequent request for public access to documents, EMA provided the complainants with its literature searches. The complainants criticised the fact that the search strategies were not included in the briefing material made available to the SAG-V experts.

56. The Ombudsman has been able to verify that the literature searches were provided to all PRAC members, as they can be found in the unredacted version of the preliminary assessment report made available to her.

57. The literature searches were not included in the preliminary assessment report provided to the SAG-V experts. The Ombudsman notes, however, that essentially all publications identified by EMA following its literature search were included in the list of **references** provided in the co-rapporteur's preliminary assessment report and were thus available to the SAG-V experts. Furthermore, the co-rapporteur provided a summary of the results of the literature search in the preliminary report that was made available to the SAG-V.

58. EMA has also confirmed to the Ombudsman that the SAG-V experts could have asked for the literature searches if they considered that they had a need for them and would have been provided with the literature searches had they requested them. EMA stated that the briefing material provided to the experts **expressly stated** that any supplementary information, such as the literature searches, was available to the experts upon request. However, no SAG-V expert requested to be provided with the searches.

59. The Ombudsman also notes that it does not seem unusual that the SAG-V experts would not have made use of that possibility. Unlike PRAC, which was responsible for the entire scientific assessment, the SAG-V experts were asked by PRAC to provide input on a number of clearly defined questions⁷⁸. In this context, given that the SAG-V experts did not ask for any additional information, the Ombudsman understands that they were provided with all the information necessary to deal with these specific questions.

Drafting of the final report

60. The Ombudsman asked EMA to explain who drafts PRAC's final assessment reports on referral procedures, such as the one on HPV vaccines.

⁷⁸ See pages 32-36 of the final assessment report.



61. EMA explained that in this case, in line with standard procedure⁷⁹, 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. Essentially, the final report is a consolidation of the rapporteur's report, the opinion expressed in writing by the scientific advisory group, as well as the PRAC's discussion and conclusions.

PRAC's comments on the research and data from a researcher and the Uppsala WHO Monitoring Centre

62. The complainants argued that PRAC's final assessment report contained "inappropriate" comments concerning the research conducted by a researcher (the researcher in question is one of the complainants). PRAC had concluded: *"Overall, the case series reported by [the researcher] is considered to represent a highly selected sample of patients, apparently chosen to fit a pre-specified hypothesis of vaccine-induced injury"*⁸⁰.

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

64. EMA argued that nothing in PRAC's position was intended to be construed as pejorative or an accusation of misconduct.

65. The Ombudsman notes that PRAC's report contains a detailed summary and extensive evaluation of the work done by the researcher⁸¹ and the Uppsala WHO Monitoring Centre⁸². The quote referred to by the complainants is part of PRAC's two-page assessment of the researcher's work. The assessment also contains further explanations on PRAC's position concerning the research⁸³. Overall, there is nothing to suggest that PRAC's comment was anything more than part of its scientific point of view on the research.

66. The Ombudsman is not in a position to evaluate the science behind the views of PRAC on the research and data from the researcher and the Uppsala WHO Monitoring Centre. However, the Ombudsman notes that, as a general rule, PRAC must be able to take a view, on an issue of science, even if that involves disagreeing with hypotheses put forward by other scientists.

b. On transparency and openness

Confidentiality clause

⁷⁹ Article 6.2 of the PRAC Rules of Procedure, available at:

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/03/WC500139609.pdf

⁸⁰ Page 24 of the final assessment report.

⁸¹ Pages 21-24 of the final assessment report.

⁸² Pages 26-29 of the final assessment report.

⁸³ Page 23 of the final assessment report: *"It is clear from the first paper that patients were excluded if they do not meet a pre-defined hypothesis of vaccine-induced illness (symptoms prior to vaccination, onset greater than 2 months after vaccination, unknown onset time or if other causes could be found). Patients were included in the third paper based only on voluntary responses to a questionnaire. The consistency in symptom profile across the case series is highlighted in the papers. However, it is unclear whether or not the absence or presence of specific symptoms was solicited by the interviewer, although the presentation of results suggests this was the case. If so, then it is perhaps not surprising that such a selected case series interviewed retrospectively in this way would yield these symptom characteristics."*



67. The complainants took issue with the fact that EMA imposes a life-long duty of confidentiality on its experts.

68. In its response to the complainants, EMA argued that it was required to do so by law: experts “*shall be required, even after their duties have ceased, not to disclose information of the kind covered by the obligation of professional secrecy*”⁸⁴. However, EMA stated that that “*the 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 and that they do not disclose commercially confidential information*”.

69. The complainants argued that the wording of EMA’s standard confidentiality clause does not seem to support this.

70. The Ombudsman acknowledged the complainants’ argument and suggested to EMA that it consider adapting its standard confidentiality clause for experts (the “Confidentiality Undertaking template”) so that it reflects better EMA’s position expressed in its reply to the complainants. EMA stated that it has initiated a review process of the template to that end, which was currently ongoing.

71. The Ombudsman concludes that EMA is in the process of addressing this point and asks EMA to inform her of the outcome of this process.

Access to documents

72. In response to a request for public access to documents, EMA provided the complainants with the minutes of the SAG-V meeting on HPV vaccines. The complainants, however, argued that if EMA “*genuinely wanted to be open and transparent, it would have provided a list of **all available documents** in the HPV vaccine case, alongside its official 40-page report on its website*” (emphasis added).

73. The Ombudsman notes that EMA already publishes a significant number of documents in relation to its procedures⁸⁵. Concerning the referral procedure on HPV vaccines, this included the Commission’s notification launching the procedure, the list of questions to the MAHs, the timetable for the procedure, the final assessment report and the meeting minutes of PRAC and the CHMP where the referral was discussed and the final conclusions adopted⁸⁶.

74. During the inquiry, the Ombudsman nevertheless suggested that EMA 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.

75. Unfortunately, EMA did not address this suggestions in its reply to the Ombudsman. The Ombudsman thus repeats her suggestion in her decision closing her inquiry. As an

⁸⁴ Article 76 of Regulation 726/2004.

⁸⁵ An overview of which documents are published is available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000169.jsp&mid=WC0b01ac0580a45420

⁸⁶ See *Overview of the referral procedure*.



alternative, the Ombudsman suggest that EMA consider other ways of assisting citizens in identifying the documents they wish to obtain. For example, EMA could state clearly that citizens requiring more information before submitting a request for public access to documents can obtain such information by first making a request for information that will be handled promptly.

Requested meeting minutes

76. As mentioned in paragraph 15 of the background, the complainants requested public access to the minutes of the SAG-V, the expert group consulted by PRAC during the referral procedure. EMA provided the complainants with a copy of these minutes. However, the complainants disagreed with EMA's decision to redact the names of certain staff members from the requested document.

77. The Ombudsman 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.

78. The Ombudsman considers that there is no necessity to disclose personal data of staff members who provide secretarial support. The decision to redact these names, but not the names of other relevant persons, was thus appropriate.

c. On alleged conflicts of interest

Availability of declarations of interest on EMA's website

79. The complainants expressed concerns that the declarations of interests of two SAG-V members were missing from EMA's online expert database⁸⁷. The Ombudsman asked EMA to provide her with copies of these two declarations.

80. In response, EMA provided the two declarations, which the Ombudsman forwarded to the complainants. EMA also explained why these declarations had been 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). The two experts in questions did not declare any interests and their full participation in the work of the SAG-V was thus legitimate.

81. EMA has thus settled this aspect of the complaint.

The conflict of interest assessment of SAG-V's scientific experts

82. The complainants criticised the evaluation of possible conflicts of interest of EMA's experts. Apart from criticising EMA's general policy on conflicts of interest, they also called into question the specific assessment concerning certain SAG-V experts⁸⁸ that had

⁸⁷ Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/landing/experts.jsp

⁸⁸ The SAG-V members, experts selected according to their specific expertise, are appointed by the CHMP (see Article 16 of the CHMP's Rules of Procedure, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500004628.pdf).



taken place before the group's meeting on HPV vaccines. The complainants disagreed with the decision to exclude certain experts but not others.

83. First, the Ombudsman notes, by way of background, that EMA's policy on the handling of competing interests of scientific committees' members and experts has since been updated⁸⁹.

84. Second, the Ombudsman has carefully assessed the cases referred to by the complainants. The Ombudsman's notes the following: Any SAG-V expert who had declared to EMA that he or she had current financial interests (for example shares) in any pharmaceutical company, and any expert who had declared other interests linked specifically to HPV vaccines (for example, former consultancy or current research on HPV vaccines), was not allowed to participate in the final conclusions and voting of the SAG-V meeting on HPV vaccines. This was in line with EMA's conflict of interest policy at the time⁹⁰, and the Ombudsman agrees that it was appropriate not to allow such experts to participate.

85. The chair of the SAG-V had declared, in his publicly available declaration of interests, that he had previously carried out, for some of the MAHs of HPV vaccines, research work on vaccines **other than HPV vaccines**. The expert did not declare any relevant current interests, neither financial nor otherwise. The Ombudsman notes that EMA's conflict of interest policy allows for such an expert to participate fully in a meeting. There is no evidence that the expert's previous research work established any form of dependence on the producers of HPV vaccines. There is also no evidence that the research done for those companies had any link to the subject under discussion, which was the safety of the HPV vaccine.

86. The complainants also take issues with public statements made by the chair of the SAG-V in the weeks before the meeting on HPV vaccines. According to the complainants, the statement was about "*the many lives [HPV vaccines] saved and [the expert] said there was no evidence of safety problems*". The complainants argue that this indicates bias on the part of this expert.

87. The Ombudsman notes that it is not unusual for an expert involved in a scientific assessment to express opinions publicly on scientific subjects that 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. 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.

88. Furthermore, the statement made by the expert seems to be common ground among the specialised public bodies, as is obvious from paragraphs 3-4 of the background, which outline the most recent review by the GACVS, the WHO's committee of independent experts. Finally, while the expert participated in the SAG-V meeting, that group simply provided advice on a number of specific, pre-defined questions. The recommendation on

⁸⁹ The new policy is available at:

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

⁹⁰ European Medicines Agency policy on the handling of declarations of interests of scientific committees' members and experts, EMA/626261/2014, Corr. 1.



HPV vaccines—that the vaccines do not cause CRPS or POTS—was taken by PRAC and the CHMP, not the SAG-V.