



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/408257/2016
Deputy Executive Director

Dear Prof Gøtzsche

Subject: Your letter of complaint dated 26 May 2016 to the European Medicines Agency (EMA) over maladministration at the EMA.

I refer to your letter of complaint sent to Prof Rasi concerning maladministration at EMA. This reply addresses all the issues you have raised with the exception of point 4 of the section "Conflicts of interest" and a number of allegations on page 17 in the section "Final remarks", which have been addressed in a separate letter provided to you, dated 17 June 2016 (Doc Ref. EMA/397114/2016).

Before going into detailed explanations (see Annex) we would like to provide some general remarks on your serious allegations.

EMA continuously strives for the best possible evidence – which we trust you support as well – in order to ensure that its scientific assessments are robust and of the highest possible quality so that EMA can meet its mission of safeguarding public health. This means that, as for any other medicines, also in the case of the safety review of HPV vaccines, the benefits will have to (continue to) outweigh any risks associated with HPV vaccines. Therefore, any additional data which moves up the evidence base is important to further substantiate the benefit/risk balance. EMA, therefore, is somewhat surprised that – different to your previous approach – you appear to now overestimate the value of studies that have important limitations such as lacking a comparator group. EMA also would like to stress that the use of HPV vaccines is expected to prevent many cases of cervical cancer, which is responsible for over 20,000 deaths in Europe each year, and various other cancers and conditions caused by HPV. In this respect, recent research published in 'Clinical Infectious Diseases Advance Access' looked at 58 studies in 9 countries from 2007 to February 2016 and showed a nearly 90% decrease in HPV infection, anogenital warts and cervical lesions in countries with the highest vaccination rates¹.

The review process in place at EMA is robust and multifaceted and it brings together scientific experts from across Europe ensuring a comprehensive, transparent and independent review. Highly experienced regulators and experts in medicines from all Member States take part in this process and any outcome is the result of a collective approach which minimises the risk of bias. Information provided by pharmaceutical companies is a vital component throughout the evaluation process of medicines worldwide, both before and after marketing. Without it, it would be impossible to provide EU patients with timely access to vital medicines currently available to them. Nonetheless, stringent legal

¹ S. M. Garland, S. K. Kjaer, N Muñoz et al. *Clin Infect Dis.* (2016)
<http://cid.oxfordjournals.org/content/early/2016/05/26/cid.ciw354.full.pdf+html>



and regulatory safeguards are in place to ensure that any information presented by pharmaceutical companies is scrutinised and independently assessed. However, it is important to highlight that the data submitted by pharmaceutical companies is only a part of the data assessed by the EMA scientific committees. The EMA takes into consideration all available information gathered independently through literature and database searches, inputs from expert meetings, advisory groups, scientific committees and working parties, patients and healthcare professionals, or any other data made available to EMA by third parties. Any evidence is assessed in a factual, scientific and objective way.

These high standards were adhered to in the EMA handling of the safety of HPV vaccines. All the evidence provided by experts, which constituted a significant element of all data assessed, was given equal consideration and this included the publications of Dr Louise Brinth and colleagues, the Danish Health and Medicines Agency and the Uppsala Monitoring Centre.

Any scientific recommendation reached by one of the EMA scientific committees is always summarised in the published assessment report. Although the published report cannot contain all the data that the scientific committee looks at, it is a comprehensive summary of all the data assessed, which highlights the most relevant evidence in support of the scientific committee's conclusions. In addition, EMA makes all available information that it holds accessible upon request. Before release of any such documents, EMA has to ensure to meet its legal duty to protect the privacy of clinical subjects and any commercially confidential information. This means that wherever necessary some information will be redacted to protect individuals as well as intellectual property.

EMA has clear rules on the handling of potential conflicts of interests of scientific committee members and experts which have been in place for many years and which are regularly reviewed and have been strengthened over time to ensure that experts and scientific committee members do not have any interests, financial or other, that could affect their impartiality. Similar arrangements exist for EMA staff. In this context we would like to refute the allegations made against Prof Guido Rasi and Dr Julie Williams as they are unsubstantiated and false. A detailed explanation is given hereafter as well as in the separate letter dated 17 June 2016. EMA's approach to conflicts of interests is a balanced approach aiming to effectively restrict the involvement of experts with possible conflicts of interests in the EMA's work while maintaining EMA's ability to access the best available expertise. We would like to confirm that the declarations of interests and curriculum vitae of all experts are published on the EMA's website in the interest of transparency and to foster trust in the regulatory system.

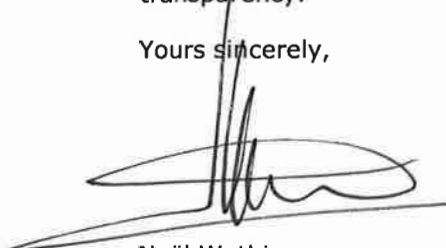
As I am sure you understand confidentiality allows reviews to be carried out without undue external influences. However, the need for life-long confidentiality can by no means be compared to an imposition of life-long secrecy as it does not prevent experts who disagree with a collegial decision to discuss their disagreements in public, provided that they shall make clear that the views expressed are their own and not those of the concerned scientific committee, and that they do not disclose commercially confidential information.

We would like to stress that transparency is at the heart of EMA and that EMA has been at the forefront of efforts to continuously increase transparency about medicines regulation; we believe it helps to ensure that the general public receives the necessary information to make informed decisions. The latest milestone in EMA's ongoing efforts to increase transparency is the imminent publication of clinical data for medicines that have been evaluated by EMA, with the first clinical reports expected to be published as of September 2016 onwards.

Please rest assured that EMA constantly monitors the safety and effectiveness of these vaccines, as with all medicines, it will continue to assess any new information as it becomes available, and will consider any regulatory action as considered needed on the basis of such new information.

We trust that the information and clarification provided has adequately addressed the points raised in your letter and we hope that our response supports EMA as a scientific body that is open and accountable to EU citizens. Please also note that EMA will publish this reply for the sake of transparency.

Yours sincerely,



Noël Wathion
Deputy Executive Director

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Annex

This annex addresses point by point the issues raised in the complaint letter.

First some clarification is provided on the terminology used in the EMA response.

The PRAC assessment report referred to in the EMA response is the report that summarises the PRAC assessment and conclusions and is published on the EMA website. This is referred to in the complaint letter as the "official EMA report".

The "Briefing note" referred to in the EMA response is the document that is provided to the scientific advisory group (SAG) participants detailing the procedural aspects and steps, with the (Co)-Rapporteurs' Preliminary assessment reports as attachments.

Outline of the case

Firstly the EMA would like to outline the procedural steps of a referral review, the documents that are produced at the different steps and their purpose.

For every safety referral, EMA and its scientific committees follow certain procedural steps which are clearly defined. Questions and answers regarding the operational aspects of the procedure are published on the EMA website.

In particular, the published timetable for the referral procedure on HPV vaccines outlines the procedural steps and their timing².

Once a safety referral is initiated, the EMA Pharmacovigilance Risk Assessment Committee (PRAC)³, which carries out the assessment, nominates from among its members so-called (Co)-Rapporteurs who take the lead in the scientific assessment and who have the task of thoroughly assessing the data and draft their recommendations which is then shared with all PRAC members. In the case of the HPV vaccines, the PRAC appointed the UK PRAC member Julie Williams as Rapporteur, as well as two Co-Rapporteurs, Qun-Ying Yue, the Swedish PRAC member and Jean-Michel Dogné, the Belgian PRAC member. When appointing (Co)-Rapporteurs their and their team's scientific expertise is taken into consideration.

As a first step, the PRAC prepares a list of questions (LoQs), which is sent to the marketing authorisation holders (MAHs), and should be answered within a certain timeframe depending on the urgency of the matter. Once adopted at the start of a procedure the LoQs is published.⁴

Once the MAH(s) submits the responses these are shared with every member of the PRAC. In the case of the HPV vaccines members also received the results of the EudraVigilance search, the published literature review including the Brinth articles, and any additional data (Danish report which included UMC data, Dutch LAREB report and data submitted by the public). Based on the responses each (Co)-Rapporteur prepares a preliminary assessment report, which is made available to all committee members to comment. In case a scientific advisory group (SAG) is held the preliminary assessment reports are shared with the SAG as part of the Briefing Note. In case of the HPV vaccines the SAG

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

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PRAC

http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000537.jsp&mid=WC0b01ac058058cb18

4

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

Vaccines was convened, which is a standing group of leading experts in the field of vaccines and vaccine safety. It was created in 2012 to provide the EMA scientific committees (e.g. CHMP or PRAC) with an expert view to complement the expertise of the regulatory network (i.e. the scientific committees and their working parties). Its composition is fixed but on a case by case basis it can be complemented with *ad hoc* experts (non-core members) in a particular disease or with expertise on an issue for which the committees requested advice. The final composition of the SAG depends on experts' availability and on their declared conflicts of interests. The final list of experts is endorsed by the committee(s).

In case of the HPV vaccines, the SAG conclusions were made available to all PRAC members. The SAG Chair reported back to the PRAC and all members had the opportunity to raise questions about the discussions and conclusions of the SAG, as per the process. In addition, the SAG conclusions were taken into account in the (Co)-Rapporteurs Updated assessment reports which were also made available to all PRAC members and to the MAHs.

For any of the steps, the assessment reports set out only the preliminary conclusions of the (Co)-Rapporteurs at that point in time. These reports 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, and are developed on the basis of the overall body of evidence available at that moment.

In its evaluation the PRAC reviewed published research including the Brinth articles, data from clinical trials and reports of suspected side effects from patients and healthcare professionals, as well as epidemiological data supplied by EU Member States (Danish report which included UMC data, Dutch LAREB) and from EudraVigilance (the European pharmacovigilance database) in relation to the complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS). The PRAC also took into account the SAG Vaccines responses to the PRAC questions, and also detailed information received from the public including a number of patient groups.

The PRAC reached its scientific recommendation by consensus following plenary discussion. This recommendation was presented in the final PRAC assessment report which summarised all the data assessed by the committee in support of the PRAC conclusions. The PRAC recommendation was subsequently forwarded to the Committee for Medicinal Products for Human Use (CHMP) who issued its opinion following a review and a plenary discussion. Finally the Commission Decision was issued by the European Commission and the referral procedure was concluded.

It has to be noted that all the documents generated during the review are considered confidential during the course of the procedure. However, they are available upon request (via the access to documents route) once the procedure has concluded and the European Commission has issued its final decision. Through this process, EMA has repeatedly made these documents available to members of the public since the conclusion of the procedure.

In relation to the Brinth *responsum* cited in your letter, please note that EMA did not receive this document from Dr Brinth directly but was made aware of it by the Danish Medicines Agency (DHMA).

Brinth's observations

1. Some of the comments made in the Brinth *responsum* document suggest that there are several aspects of the PRAC discussion regarding the Brinth publications that appear to have been misunderstood; for example, the methodology of case series has important limitations as it lacks a comparator group and is also known to be vulnerable to selection bias, regardless of who conducts the analysis. The latter remains an issue with these case series despite efforts to minimise this; another

example is the potential of misinterpretation of data due to the likelihood of recall bias, which is something inherent to the methods used, and is partly driven by patient awareness. EMA respectfully disagrees with your claim that “EMA’s allegations constitute guesswork (“apparently”), are pejorative and come close to an accusation of scientific misconduct”. EMA’s position, as discussed above, is not based on “guesswork” but rather objective considerations. Moreover, nothing in the EMA’s position is either intended to or may be construed as pejorative or an accusation of any type of misconduct.

2. Regarding the Uppsala Monitoring Centre (UMC) analysis, note that their data is based on VigiBase (the WHO Global ICSR Database System), which includes spontaneous reports. Although there is an imbalance in the absolute numbers of reports of POTS/CRPS with HPV versus non-HPV vaccines, the difference was not statistically significant and only when a lowered threshold for significance was used were ‘asthenic conditions’ HLT (High Level Term) significantly different. The PRAC assessment reflects these findings of interpretation of the data in the UMC analysis. The EMA committees raise limitations with studies, regardless of who conducted them, and regardless of whether those are inherent limitations in the chosen methodology.

Further remarks on different levels of reporting between countries are included in the PRAC assessment report. Increased media attention was proposed as a potential cause for the imbalance in reporting; the pharmacovigilance centre LAREB data report independently proposed this explanation, as well as the experts convened in the SAG Vaccines.

3. In this point the EMA report may have been misunderstood; the phrase “Chronic fatigue syndrome (CFS) has been reported constantly since 2009”, means that the event has been continuously recorded over a period of time and does not contain a judgement on the intensity of the reporting.

4. Regarding your comment about discrepancies between EMA and the Danish reports in the way adverse events were classified please note that the PRAC has used the GVP definition of serious adverse events (SAEs) in order to classify the adverse events: “An adverse reaction which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect”. Most symptoms of CRPS and POTS are non-specific, meaning that they are difficult to diagnose both in the general population and in vaccinated individuals and some symptoms may overlap with chronic fatigue syndrome (CFS). Many of the reports of POTS considered in the referral have features of chronic fatigue syndrome and some patients have been diagnosed with both POTS and chronic fatigue syndrome, an observation which was also supported by recent publications (Brinth et al, 2015). Indeed, reports of other symptoms/signs were also taken into consideration, provided that there was a suspicion of POTS or CRPS in line with the scope of the referral.

For this analysis, reports that did not fully meet the diagnostic criteria for these syndromes were also considered also taking into account underreporting. A very conservative approach was used including also reports that may not have been true POTS or CRPS under the definitions. Even with this approach no link to the vaccines could be identified. One element that emerged clearly from this assessment is that individual cases did not show a consistent pattern regarding time-to-onset following vaccination or clinical characteristics.

5. As explained above, the SAG Vaccines was consulted on specific questions that the PRAC put to them. The SAG does not release any minutes document after its meeting, however both the PRAC questions and the SAG responses are inserted *verbatim* in the PRAC assessment report published on the EMA web site⁵.

Divergent views are only reflected in the document where consensus cannot be reached on a given question. In the case of the HPV vaccines referral, all SAG experts who were allowed to contribute without restrictions endorsed the final responses by consensus. Experts with declared interests could only participate during the discussion and were neither allowed to contribute to the final conclusions of the SAG nor comment on the written SAG response document. This is in line with, and further detailed in, the Mandate, Objectives and Rules of Procedure document of the SAG, which was followed as usual. This document is available on the EMA website together with other supportive documents⁶.

In order to reach its conclusion that the evidence does not support that HPV vaccines (Cervarix, Gardasil, Gardasil 9, Silgard) cause CRPS or POTS, PRAC took into account the totality of the available information and this is reflected in the assessment report. The benefits of HPV vaccines therefore continue to outweigh their risks. The PRAC focused specifically into looking closely at CRPS and POTS in this review. As regards your comment that "the minutes of the [EMA] meetings are not released", this is incorrect: documents held by EMA are either proactively published on our website (including minutes of CHMP and PRAC meetings) or released in response to requests for access to documents, subject to the exceptions set out in Article 4 of Regulation (EC) No 1049/2001. This also applies to documents from SAGs. EMA cannot, therefore, agree that "*this [is] a very strange, unscientific and undemocratic approach*".

As the European Commission asked the PRAC in the Notification letter whether any other measures needed to be considered, it is the responsibility of the PRAC, the (Co)-Rapporteurs, and all the members to discuss this question and give its opinion. The PRAC specifically asked the SAG Vaccines to discuss the feasibility of performing further studies with the potential to provide robust and meaningful results within existing data sources in Europe. The response from the SAG Vaccines is included *verbatim* in the PRAC assessment report⁷ as mentioned above. The SAG response does not preclude any other research centre, academic institute or national authority from conducting its own studies, should they decide to do so. It should be noted that it is outside of EMA's (or its committees) remit to recommend public health authorities to conduct (or not) research studies in any field.

The EMA respectfully disagrees with your opinion that a life-long obligation for professional secrecy imposed on experts participating in EMA working groups and scientific advice groups is "extreme", "absurd", illegitimate and contrary to public interest and undermining the legitimacy of the EMA.

The professional secrecy obligation is set forth in Article 76 Regulation (EC) No 726/2004, which governs the activities and functioning of EMA. This obligation is imposed on EMA staff, members of the EMA Management Board, members of EMA scientific committees and experts, including experts who are members of SAGs and *ad hoc* expert groups established to provide scientific advice experts views in relation to ongoing regulatory procedures, such as the HPV referral in question.

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(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)

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

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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

Article 76 explicitly provides that the obligation for professional secrecy applies “*even after their duties have ceased*”. This Article reflects the more general secrecy obligation imposed on all EU officials, including EMA staff, by Article 339 of the Treaty on the Functioning of the European Union not to disclose information of the kind covered by the obligation of professional secrecy, even after their duties have ceased. The above confidentiality obligations are transposed and further clarified by Article 17 of the “Regulations and Rules applicable to officials and other servants of the European Union (Staff Regulations)” and the “EMA Guidance on Confidentiality and Discretion” (Section 3 of the EMA Code of Conduct).

However, we argue that there are two common sense exceptions to the above rule: a) the relevant information may become public at some point in time and the secrecy obligation would thus become devoid of its purpose; b) 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. This last remark should hopefully address your observations concerning “*a life-long secrecy clause that prevents them [the experts] from discussing their disagreements in public*”.

6. Regulatory agencies work by assessing data provided by pharmaceutical companies, in addition to any other available evidence irrespective of the source of information. Pharmaceutical companies have legal obligations to fulfil when submitting data to regulatory agencies for review and this is defined in the legislation. The MAHs are the owners of data from clinical trials and data in their safety databases; these data are crucial in any assessment and cannot be ignored. For any referral procedure the data submitted by the pharmaceutical companies will always be assessed by the (Co)-Rapporteurs who then do their own assessment, may ask additional questions or pose requests for further analysis/data to the MAHs. This is described in the Q&As documents regarding referral procedures. As mentioned above, in case of the HPV referral, the responses to the LoQs from the PRAC were submitted by the MAHs to all PRAC members. In the questions, the MAHs were asked specifically to analyse the data and provide an evaluation of the results.

The data submitted by the MAHs is only one part of the data assessed by the Committee. A search of the EudraVigilance database and the published literature were also conducted independently by EMA and by the assessing teams, and have been discussed thoroughly during the procedure. It may be noted that some of the data may overlap, for example EudraVigilance may contain individual case safety reports submitted by MAHs, as well as others.

All data reviewed by the PRAC can be made available to the public following requests for access to documents, as per the EMA policy.

7. All PRAC members had the opportunity to comment in writing during the commenting phase (see timetable of procedure). In addition PRAC members had the opportunity to discuss any concerns they might have had in the plenary PRAC meetings at the start of the procedure (July 2015), at the time of adoption of the questions to the SAG Vaccines (Oct 2015) and at the conclusion of the procedure (Nov 2015). SAG responses to questions are always made available to committee members, and, as is always the case, PRAC members had the opportunity to question the SAG chair in person when he presented the SAG responses to the PRAC plenary meeting. Moreover, Rapporteurs for the referral, assessors and other members of the PRAC attended the SAG Vaccines meeting in person and had the opportunity to ask any questions to participants, including to pharmaceutical companies.

It needs to be emphasised that every decision taken by the PRAC -and this is the case for any EMA committees- is a collective decision. This can be reached by majority if there are members that do not agree with the majority conclusions, or by consensus. Members that do not agree with the majority conclusions have to justify the grounds for their divergent position, which are then made public. In this case the PRAC recommendation was adopted by consensus, and any questions or outstanding issues were resolved, which is why the procedure could conclude.

The MAHs' review of post-marketing reports was based on data from the MAHs' pharmacovigilance databases, which include spontaneous reports from healthcare professionals and consumers. It is common practice that when a report is received, the MAH contacts the reporter and tries to retrieve as much medical information as can be shared. However, access to full medical records is not usually granted by treating physicians to manufacturers of medicinal products. A wide strategy to identify potential cases was employed, in addition to identifying reports with an established diagnosis of POTS or CRPS (see also response to point 8 below).

8. It is acknowledged that POTS is characterised by a constellation of symptoms. The PRAC noted that most symptoms of CRPS and POTS are unspecific, making them difficult to diagnose both in the general population and in vaccinated individuals. The PRAC report clearly states that in order to identify possible cases of undiagnosed CRPS and POTS, the MAHs were requested to use common search strategies, which also used an algorithm to identify reports with combinations of signs and symptoms common in CRPS or POTS, even if the reports did not include an established diagnosis of POTS or CRPS. This strategy is meant to retrieve more cases, not fewer, which is the conservative approach used in pharmacovigilance. There seems to be a misunderstanding in Brinth's statement and in the comment from the requester: the word "common" is used in the report as *"shared by two or more people or things"*, not as *"occurring, found, or done often"* i.e. the search strategies were shared between the MAHs to enable the comparison of data.

The clinical details of all reports were individually evaluated by the MAHs to determine if the established criteria of CRPS and POTS were fulfilled, and then reviewed by the (Co)-Rapporteurs. The MAHs were asked to clearly describe case detection methods and discuss whether the reported cases fulfilled published or recognized diagnostic criteria. In the case of POTS the Sheldon and colleagues (2015)⁸ publication and that of Raj (2013)⁹ were used for the case definition. During the review of the data provided by the MAHs, the (Co)-Rapporteurs assessed case detection methods for each MAH. Further details on the broad, common search strategies are included in the (Co)-Rapporteurs' assessment reports, previously released and available upon request.

9. For both Cervarix and Gardasil, all studies submitted for the marketing authorisation application were placebo controlled. Placebo consisted in most studies of aluminium-containing solution or of a hepatitis B vaccine (Recombivax HB, used in Gardasil development) or a Hepatitis A vaccine (Havrix, used in Cervarix development).

Study 018 for Gardasil investigated almost 700 subjects using an inactive placebo. The study's primary objective was to evaluate the safety of Gardasil among 9- to 15- year-old boys and girls. This study allowed the comparison of Gardasil with a non-aluminium-containing placebo (all other studies compared the vaccine with aluminium containing placebo, as mentioned). Subjects were also evaluated

⁸ Sheldon et al, (2015) 2015 heart rhythm society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. Heart Rhythm 12(6): e41-63.

⁹ Raj SR, (2013) Postural tachycardia syndrome (POTS). Circulation. Jun 11;127(23):2336-42.

for new medical conditions 1 year post vaccination. The data from study 018 was compared with the safety of the antigens and adjuvant as evaluated in the rest of the clinical trials.

Overall there was no significant increase in the reactogenicity following Gardasil vaccination as compared to the non-aluminium containing placebo administration. Local pain, headache, nausea and pyrexia were the most common symptoms observed in both groups. The only major difference noted between aluminium containing placebo and placebo without aluminium was the rate of local pain which was less frequent after non-aluminium-containing placebo administration (45.4% in non-aluminium placebo vs. 75.4% in aluminium-placebo).

For both vaccines development, the use of $\text{Al}(\text{OH})_3$ (500 μg) rather than a true placebo (inactive control) was found acceptable by the CHMP in order to maintain the double blinding of the studies and consequently the validity of data. The use of an active control as placebo (i.e. an unrelated vaccine) was found acceptable from an ethical perspective especially in trials involving children since it confers benefit to subjects randomised to the control group.

The approach taken for both vaccines was found by the CHMP as a reliable way to establish the safety profile of the vaccines at the time of authorisation.

The safety of aluminium as adjuvant is considered well characterised based on data from clinical trials and decades of use with several antigens in different types of vaccines licensed worldwide. On the basis of the scientific assessments performed over the years by EMA¹⁰ and other experts such as from EFSA¹¹, FDA¹² and WHO^{13,14}, the scientific evidence available to date continue to support the safe and effective use of aluminium adjuvants in vaccines.

In addition non-clinical studies for HPV vaccines, such as conventional studies of safety pharmacology, acute and repeated dose toxicity, local tolerance, fertility, embryo-foetal and postnatal toxicity revealed no potential risk for humans.

Concerning POTS and CRPS, in the review of clinical trial data done for the referral, a total of 60,594 subjects were included for Gardasil/Silgard and Gardasil 9 and 42,047 subjects for Cervarix. No cases of POTS or CRPS were identified in the Cervarix and comparator cohorts. The incidence of POTS and CRPS in the Gardasil/Silgard and Gardasil 9 clinical trials was less than 1 case per 10,000 person-years and comparable in the Gardasil/Silgard/Gardasil 9 and corresponding placebo cohorts, showing that, irrespective of the comparator used, the incidence of POTS and CRPS was very low in the vaccinated group and in line with the estimated incidence of POTS and CRPS in the general unvaccinated population.

10. It is acknowledged that the calculation of the background incidence rate in the relevant age population is difficult. The background incident rates for CRPS were calculated in reference to de Mos and colleagues (2007)¹⁵. The PRAC used all the available scientific data to reach its conclusions in a fact-based approach. At the same time, PRAC also acknowledged that given the complexity of the syndrome and likely differential practice in approaches to diagnosis and management across countries and centres, reported background incidence may differ between countries.

In reference to the Brinth *responsum*, it is highlighted that there are possibly many more cases that have been referred to the Syncope Unit (the figure of 650 included in figure on page 16), but no

¹⁰ http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/07/WC500108657.pdf

¹¹ <http://www.efsa.europa.eu/en/efsajournal/pub/754.htm>

¹² <http://www.fda.gov/BiologicsBloodVaccines/ScienceResearch/ucm284520.htm>

¹³ http://www.who.int/vaccine_safety/topics/aluminium/statement_112002/en/index.html

¹⁴ http://www.who.int/vaccine_safety/reports/Jun_2012/en/index.html

¹⁵ de Mos et al, (2007) The incidence of complex regional pain syndrome: A population-based study, Pain; 129, 12-20.

further information on these cases and whether or not they occurred in HPV vaccinated individuals have been provided. However, the observed versus expected scenarios for Denmark suggested that the 650 figure included by Dr Brinth is within the range of expected scenarios. Furthermore, as both POTS, CRPS and Chronic fatigue syndrome (CFS) are issues that remain under close scrutiny and will be subject to updated observed versus expected analyses, any further cases reported to regulatory authorities or the MAHs will be factored into future regulatory assessment and decision making.

The approach taken in this referral procedure by applying the observed versus expected analysis allowed the PRAC to use the most sensitive detection of a possible excess of the natural background rates and account for a range of possible under-reporting up to 99%. It should be noted that the PRAC took into account the data from Uppsala Monitoring Centre (UMC) report accordingly.

11. A literature review was conducted by the EMA and in addition by the Rapporteur's teams; the publication search criteria used included the names of the syndromes and the presence of either the mention of the words "vaccine" or "HPV", with associated synonyms.

The list of the publications taken into account has already been released to requestors for access to documents. In the PRAC assessment report, only the most relevant and the most important publications have been referred to, and this list is a subset of the overall list of the publications that have been considered.

EMA respectfully disagrees with your claim that *"EMA has ridiculed and dismissed the research performed at the Danish Syncope Unit in a way that is unfair, misleading, partly erroneous and pejorative"*. As already mentioned above, limitations of the studies should be mentioned even when those are innate shortcomings of the methodology used. EMA's position is objective and based on scientific evidence. Nothing in the EMA's position is either intended to or may be construed as pejorative.

Many redactions by the EMA in its documents are not legitimate

All access to documents requests regarding documents related to the referral on HPV vaccines have been processed in accordance with Regulation (EC) No 1049/2001 regarding public access to European Parliament, Council and Commission documents (the Regulation)¹⁶, the Rules for the Implementation of Regulation (EC) No 1049/2001 on access to European Medicines Agency documents (the Agency rules)¹⁷ and the European Medicines Agency policy on access to documents related to medicinal products for human and veterinary use (the Agency policy)¹⁸.

According to the Regulation, EMA can refuse access to documents or redact parts thereof, if one or more of the exceptions provided in Article 4 are applicable. EMA has reviewed the documents released and can confirm that all redactions made in the documents are in accordance with the requirement of the Regulations, in particular Article 4, and in line with the EMA's Policy and Rules. Below are the specific details concerning each of the redactions:

- In accordance with Article 4(1)(b) of the Regulation and the European Union legislation regarding the protection of personal data, all protected personal data were redacted in order to avoid that the disclosure of the document would undermine the privacy and integrity of any individual. EMA, as required by the above provision, read in conjunction with Regulation (EC) No 45/2001, has redacted all health data that could lead to the identification of a natural person. EMA conducted this exercise in light of the sensitive nature of the information at stake, the applicable rule on

¹⁶ OJ L 145, 31.5.2001, P. 43-48 (<http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32001R1049>)

¹⁷ EMEA/MB/203359/2006 Rev 1 Adopted

¹⁸ EMA/110196/2006 of 30 November 2010

processing of health data laid down in Article 10 of Regulation (EC) 45/2001 and regulatory guidelines including for example the provisions of the *Recommendations on the handling of requests for access to Periodic Safety Update Reports (PSURs)*¹⁹, the minimum personal data to be deleted to ensure anonymisation of the information would require the deletion of information on date of birth, on (reporting) country, the patient identification code. Furthermore, the recommendations provide that *"it should never be possible to identify a natural person from the information disclosed"*. The position adopted by EMA takes into account the advice of the European Data Protection Supervisor (EDPS) regarding the extent to which information received for the purpose of pharmacovigilance, including adverse reactions should be considered personal data in accordance with Article 2 (a) of Regulation (EC) 45/2001.

- As a result, all relevant patient data have been redacted, e.g. patient identification numbers, case report numbers, reporting countries, site numbers and any other information that may lead to the identification of a patient in the context of a patient narrative. However, the information taken into consideration in the assessment reports which does not permit identifying individual patients has not been redacted.

EMA respectfully disagrees with your claim that "it is not possible to identify individual people from a case number". EMA would like to recall that key-coded or merely pseudonymised personal data are still to be considered personal data falling under the scope of the applicable data protection legislation. As authoritatively stated by the Article 29 Working Party, *"pseudonymisation reduces the linkability of a dataset with the original identity of a data subject, as such it is a useful security measure but not a method of anonymization"*²⁰ (emphasis added). Moreover, with regard to key-coded data processed in the context of clinical trials, the Article 29 Working Party has also stated that *"The pharmaceutical company has construed the means for the processing, included the organisational measures and its relations with the researcher who holds the key in such a way that the identification of individuals is not only something that may happen, but rather as something that must happen under certain circumstances. The identification of patients is thus embedded in the purposes and the means of the processing. In this case, one can conclude that such key-coded data constitutes information relating to identifiable natural persons for all parties that might be involved in the possible identification and should be subject to the rules of data protection legislation"*²¹. EMA is therefore obliged by the provisions of Regulation (EC) 45/2001 to take any reasonable measure to ensure that sensitive personal data are redacted from documents made accessible to the public in order to guarantee the protection of privacy of patients.

Furthermore, the EMA's practice is to redact personal data of some EMA staff involved in pre- and post-authorisation activities. Personal data includes any elements that permit the identification of EMA staff (e.g. names, email addresses, phone numbers). This is the result of a balancing exercise between the interests of transparency and the interests of the protection of privacy of individuals and in particular concerning the identity of EMA staff members that are part of the EMA secretariat and do not take part in the elaboration of the scientific opinion of the EMA scientific committees. This approach is in accordance with the case-law of the Court of Justice of the EU on the application of the provisions of Regulation (EC) 1049/2001 to documents containing personal data²² and in line with EMA's policy on access to documents and the *Output of the European Medicines Agency policy on access to documents related to medicinal products for human and*

¹⁹ EMEA/743133/2009 of 23 November 2009

²⁰ Cfr. Article 29 Working Party Opinion 05/2014 on Anonymisation Techniques, at p. 20, available at http://ec.europa.eu/justice/data-protection/article-29/documentation/opinion-recommendation/files/2014/wp216_en.pdf.

²¹ Article 29 Working Party in their Opinion N° 4/2007 on the concept of personal data - WP 136 Available at http://ec.europa.eu/justice/data-protection/article-29/documentation/opinion-recommendation/files/2007/wp136_en.pdf

²² Cfr.: Case C-28/08 P "Bavarian-Lager"

*veterinary use*²³. However, personal data relating to EMA staff with managerial and official functions is not redacted and their names and contact details are published on the EMA website²⁴.

Moreover, the names of committee members involved in the evaluation of medicinal products are considered releasable and the information is proactively published on the EMA website.

- In accordance with Article 4(2) 1st indent of Regulation (EC) No 1049/2001, commercially confidential information should be redacted in order to avoid that the disclosure of the document would undermine the protection of commercial interests of a natural or legal person, including intellectual property. In this case, doses of vaccines distributed and number of cases per country are considered confidential information regarding sales data. This is in line with the "HMA/EMA recommendations on transparency: Recommendations on the handling of requests for access to periodic safety update reports"²⁵. While global sales in the EU are not considered commercially confidential and are not redacted, sales by individual country could disclose sensitive information concerning the company's commercial and business strategies and was considered commercially confidential and redacted in accordance with Article 4(2) 1st indent of the Regulation. We would like to point out that, although mentioned in your letter, in this context country names were not redacted.
- In accordance with Article 4(3) 2nd paragraph of Regulation (EC) No 1049/2001, documents containing opinions for internal use as part of deliberations and preliminary consultations within EMA shall be refused even after the decision has been taken if disclosure of the document would seriously undermine the EMA's decision-making process. This is also reflected in the EMA's Policy under the section "Protection of internal deliberations". In this regard, EMA redacted the names of the EU Member States that submitted comments to the assessment reports. While the content of the comments themselves is not redacted, EMA does not disclose the identity of the EU Member State which made the comment. The disclosure of this information would undermine the collegial and confidential nature of the discussion and would deter the EU Member States from having open and comprehensive discussion in future procedures.
- Regarding the mentioned publication identifier for an article in press that has been redacted, this has been an error. In accordance with the Regulation (EC) No 45/2001, any requester can submit a confirmatory application to challenge the redactions made in the documents that are released. This kind of redaction could have been corrected and further explanations as to the reasons for the applied redactions could have been provided. However, it should be noted that no confirmatory application has been submitted regarding documents related to the HPV vaccines referral.

Uncertainties in science that did not make it to the official report

It is confirmed that there are indeed two Co-Rapporteurs' assessment reports, one from the Swedish Co-Rapporteur and one from the Belgian Co-Rapporteur and this is stated in the reports. The document referenced extensively in the Cochrane letter is the Preliminary assessment report by the Belgian Co-Rapporteur.

1. As mentioned above, each (Co)-Rapporteur created their Preliminary assessment report, made these reports available to all PRAC members and invited all the Member States to comment. The

²³ EMA/127362/2006 of 30 November 2010

²⁴ http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000112.jsp&mid=WC0b01ac0580028a43

²⁵ Available at

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/12/WC500016912.pdf

recommendations included in the Preliminary report are based on the initial evaluation of the data received, before considering the comments from EU Member States, and from consulted experts. The PRAC (Co)-Rapporteur has reconsidered their position following the interaction with the previously named stakeholders; this updated position was reflected in the joint report. The PRAC reached its scientific recommendation by consensus following the plenary discussion. The recommendation was presented in the final PRAC assessment report. The PRAC recommendation was endorsed by the Committee for Medicinal Products for Human Use (CHMP) who issued its Opinion following a review and a plenary discussion. The two Committees concluded that there was no evidence of a causal link between HPV vaccination and the two syndromes CRPS and POTS, at the time the referral concluded. The HPV vaccines like any other medicine carry risks. Those risks are summarised in the Product Information of the medicinal products. The information reflected in the Product Information is the result of analysis of the totality of the data made available to regulators from clinical development to use of these vaccines in millions of patients around the world. The adverse drug reactions included in the Product Information are adverse events for which a causal relationship with the vaccine was considered to be at least a reasonable possibility. So far, the benefits of the vaccines outweigh their risks in the view of the CHMP and the PRAC, as well as other regulatory authorities that have licensed the same vaccines worldwide. It is of no minor importance that all products are subject to continuous safety monitoring, and any noted concerns or changes are assessed immediately via pharmacovigilance procedures (e.g. periodic safety update reports or PSURs, or signal detection).

Kindly note that the WHO Global Advisory Committee on Vaccine Safety (GACVS), an expert clinical and scientific advisory body, has also reviewed the safety of HPV vaccines in December 2015²⁶.

2, 3 and 5. The comments quoted here are comments made by one Member State, not by the (Co)-Rapporteurs of the procedure. The comments were considered and discussed by the (Co)-Rapporteurs in their Updated assessment report. The final PRAC assessment report was adopted by consensus; therefore the Member State that raised the original comment considered that it was sufficiently addressed.

There is no explicit agreement in the assessment reports (draft or final) from the (Co)-Rapporteurs, with any of Dr Brinth's statements or with the conclusion of her publications, apart from the following: *"Taken together; it is agreed with the authors that this case series does not provide sufficient data to establish a reasonable possibility of a causal relation between the HPV vaccine and POTS."*

The PRAC as a whole taking into account the totality of the data presented, and using well-established methods for signal detection, reached by consensus its scientific recommendation. In addition the PRAC specifically recommended individual 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.

4. In the first and fourth paragraphs, the statements of the Belgian Co-Rapporteur are presented. As noted before, these statements represent the view of the Co-Rapporteur, which were then resolved in the course of the procedure as the discussion evolved and all the elements and evidence were brought together. The final PRAC assessment report was commented and endorsed by the three (Co)-Rapporteurs and ultimately by the whole PRAC, and subsequently by the CHMP. The individual (Co)-Rapporteurs' assessment reports represent the view of individual teams at intermediate phases of the procedure. They, thus, constitute interim reports, which undergo several modifications during the procedure, hence they are not published. The individual (Co)-Rapporteurs' views as reflected in the preliminary reports are then discussed among all PRAC members and the view of the whole PRAC is

²⁶ http://www.who.int/vaccine_safety/committee/topics/hpv/en/

then reflected in the final PRAC assessment report, representing a summary of the overall assessment. As already mentioned, divergent views are always reflected in the final report, should any be raised.

Specifically concerning the criticism on the preliminary divergent view of the Belgian (Co)-Rapporteur which was subsequently changed and reflected differently in the joint report, it should be clarified that in their preliminary assessment, the Belgian (Co)-Rapporteur considered that the evidence did not permit either to conclude or to exclude an association with CRPS and, based on this preliminary view, proposed a PASS to gain further evidence on the potential association. The SAG experts considered a PASS although feasible to be conducted, was unlikely to produce robust results given the difficulties in identifying the cases and the potential biases. Taking into consideration this element and the overall SAG discussion, as well as their updated view on the causality assessment, the Belgian Co-Rapporteur reconsidered the need for a study to be requested from the manufacturers.

For second and third paragraphs, please see response to points 2, 3 and 5 above.

6. The views expressed by the (Co)-Rapporteurs and by the PRAC with regard to the Brinth data represent a critical assessment of the data and the type of study from a purely scientific perspective. and in no way it is intended to undermine -or endorse- the credibility of any expert. Such views may or may not be shared by all parties, but nevertheless they remain the views of the PRAC.

7. In this point the Cochrane letter presents the view of members of public who submitted spontaneous information which were included in the Belgian Co-Rapporteur's assessment report. This reinforces the general position and the common practice that all data submitted in relation to this review have been shared with all PRAC members and was assessed, regardless of the source of the information.

It is not the position of the EMA and its committees that the HPV vaccines are without any risk, nor would this be true for any medicinal product that is on the market. As already clarified, it is a matter of balance between benefits and risks and it is acknowledged that the evaluation needed to conclude on this balance can be extremely complex. Moreover presenting in a short report how the whole of the available evidence has been assessed and weighed to reach those conclusions may also be complex. EMA is striving to always improve the quality and clarity of its assessment reports to ensure maximum transparency, so that the European public can see how decisions were made. It also aims to fairly represent the open and thorough way in which European experts work at EMA.

Conflicts of interest

1. The EMA has thoroughly and critically reviewed the data and analyses presented by the MAHs, and all other information available. This means an in-depth assessment which is performed by multiple experts who can ask for any clarification or additional information that is required. Moreover, EMA also relied on various confirmatory sources of information such as published literature and data from pharmacovigilance databases.

Companies have the legal obligation to provide all available data they have in their possession to the regulatory authorities and there are mechanisms in place to ensure that this is abided by.

2. EMA takes due care to ensure that its scientific committee members and experts, including SAG members and experts, do not have any financial or other interests that could affect their impartiality.

EMA has a policy²⁷ on the handling of declarations of interests of scientific committees' members and experts.

²⁷ http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/10/WC500097905.pdf

Each expert has to make a declaration of interests (annually or earlier if their interest change) which EMA's secretariat scrutinises and assigns an interest level based on whether the expert has any interests in pharmaceutical industry, and whether these are direct or indirect.

After assigning an interest level, the level of participation in the EMA's activities is determined by 3 factors: the nature of the declared interest, the timeframe during which such interest occurred, as well as the type of activity that the expert will be undertaking.

The overall principles of the policy can be summarised as follows:

- Current direct interests in pharmaceutical industry, i.e. current employment, current consultancy, current strategic advisory role and current financial interests are incompatible with involvement in any EMA activity. There are however two exceptions:
 - i) current consultancy for an individual medicinal product and current strategic advisory role for an individual medicinal product are allowed for SAG and *ad hoc* expert group Chairs, members and experts, but restrictions on involvement apply (i.e. the expert cannot participate in any activity regarding the declared product) and
 - ii) current consultancy, current strategic advisory role and current financial interests are allowed for an expert witness who's involvement is limited to testifying and giving specialist advice on a specific issue by providing information and replying to any questions only, but with no involvement in the final discussion or deliberations on the issue.
- Past direct interests, e.g. past employment, past consultancy, past strategic advisory role and past financial interests, as well as current or past indirect interests, e.g. principal investigator, investigator, grant/other funding to organisation/institution and close family member interests are allowed, but may result in restrictions in involvement depending on their nature, their timeframe of occurrence and the type of activity.

In the interest of transparency, the declarations of interests and curriculum vitae of experts are published on the EMA's website and the outcome of their evaluation and the applicable restrictions are included in meetings' minutes.

We would like to assure you that the policy was correctly applied to the participants of the SAG meeting on HPV vaccines which took place on 21 October 2015. The declarations of interests were evaluated and restrictions on experts' involvement were applied based on the principles described above.

In line with the policy, experts who had declared current direct interests in a pharmaceutical company or for a particular medicinal product were allowed to participate in the SAG meeting:

- with restrictions resulting in either exclusion from the final deliberations or involvement as 'expert witness' (this role was limited to testifying and giving specialist advice on this specific issue by providing information and replying to any questions only), or
- with no restrictions (if the interests declared did not present a potential conflict of interest with respect to the specific topic discussed at this SAG meeting)

Experts who declared past direct interests and indirect interests were allowed to participate in the meeting with or without restrictions. Where restrictions applied (if the interests declared presented a potential conflict of interest with respect to the specific topic discussed at this SAG meeting), those experts were not allowed to participate in the final discussion and decision.

We would also like to highlight to you that the format of participation for Enrica Alteri at the hearing on HPV vaccine safety at the Danish Parliament on 17 December 2015 was agreed ahead of the hearing

with the organisers. We are surprised by your comments on Enrica Alteri's presentation since the feedback provided to EMA was that her presentation was very well-received at the hearing.

3. Regarding your comments on the PRAC Rapporteur Julie Williams, we would like to clarify that you are in error as you are referring to a totally different person of the same name.

The PRAC rapporteur Julie Williams is not a Professor of Neuropsychological Genetics at Cardiff University or the Chief Scientific Adviser for Wales as you claim and she did not co-author the article that you mentioned. The Wikipedia webpage you mention refers to a different person.

The PRAC rapporteur Julie Williams holds degrees in applied biology and nutritional biochemistry and a PhD in clinical biochemistry and she is pharmacovigilance expert assessor at the Medicines and Healthcare products Regulatory Agency in the United Kingdom where she has been employed since 1998. This information can be read in her curriculum vitae²⁸ which you can check, as it is publicly available on the EMA website, as are those for other PRAC members. In her current declaration of interest²⁹ dated 12 November 2015, she did not declare any interests in the pharmaceutical industry and therefore no conflicts of interest were identified.

The current declarations of interest of the PRAC Co-Rapporteurs Jean-Michel Dogne and Qun-Ying Yue are published on the EMA's website (Jean-Michel Dogne³⁰, dated 8 January 2016; Qun-Ying Yue³¹, dated 19 October 2015). Qun-Ying Yue did not declare any interests in the pharmaceutical industry and therefore no conflicts of interests were identified. Jean-Michel Dogne declared current indirect interest in a pharmaceutical company which did not present a potential conflict of interest with respect to the HPV vaccines and hence he was not restricted.

Finally, we would also like to clarify that EMA's code of conduct³² extends the requirements for impartiality and the submission of annual declarations of interests to all staff members working at the EMA. Potential conflicts of interests of staff members are handled by EMA in a similar way to committee members and experts. We can confirm that all EMA staff involved with the evaluation of the referral on HPV vaccines have been checked and no conflicts of interests were identified.

Final remarks

Concerning premature ovarian failure (POF) following HPV vaccination we would like to assure you that this is continuously monitored by routine pharmacovigilance activities, which includes systematic reviews of the literature, for both vaccines. For Cervarix, based on its latest PSUR the PRAC overall was of the opinion that the available data are not sufficient to characterise a potential link between HPV vaccination and POF. POF will continue to be monitored through routine pharmacovigilance activities and the PRAC will re-assess the risk of POF following Cervarix vaccination in the next PSURs. The assessment of the most recent PSUR for Cervarix is currently ongoing. Concerning Gardasil, the PRAC recommended review of relevant data/publications on POF as part of ongoing routine pharmacovigilance. The issue was thereafter evaluated in subsequent PSURs, including reviews of non-clinical and clinical studies, post-marketing data and discussions on possible mechanisms. Overall, these data did not suggest a causal association between POF and Gardasil/Silgard vaccination, to-date.

²⁸ http://www.ema.europa.eu/docs/en_GB/document_library/contacts/jwilliams_CV.pdf

²⁹ http://www.ema.europa.eu/docs/en_GB/document_library/contacts/jwilliams_DI.pdf

³⁰ http://www.ema.europa.eu/docs/en_GB/document_library/contacts/jdogne_DI.pdf

³¹ http://www.ema.europa.eu/docs/en_GB/document_library/contacts/qyue_DI.pdf

³² http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500004924.pdf