

10 October 2016

Complaint to the European ombudsman over maladministration at the European Medicines Agency (EMA) in relation to the safety of the HPV vaccines

To: the European ombudsman

From:

Peter C Gøtzsche, DrMedSci, MSc, Director and Professor, the Nordic Cochrane Centre
Karsten Juhl Jørgensen, MD, DrMedSci, Deputy Director, the Nordic Cochrane Centre
Tom Jefferson, MD, Honorary Research Fellow, Centre for Evidence Based Medicine, Oxford, UK
Margrete Auken, MEP (The Greens/European Free Alliance)
Louise Brinth, MD, PhD, Danish Syncope Unit, Frederiksberg



Supported by:

The following people and organisations support the complaint to the EU ombudsman. They are not responsible for the substance in the complaint, which it is up to the EU ombudsman to come to a decision about.

Silvio Garattini, Director, Istituto di Ricerche Farmacologiche Mario Negri, Milano, Italy
Ralph Edwards, Ex-director, WHO Uppsala Monitoring Centre, Sweden
International Society of Drug Bulletins (ISDB)
Angela Spelsberg, Chair, Working Group on Health, Transparency International, Germany
No Gracias, Independent civil organization for transparency, integrity and equity, Spain
Juan Gérvás, Visiting Professor, National School of Public Health, Madrid, Spain
Ulrich Keil, Prof. Emer., Institute of Epidemiology and Social Medicine, Univ. of Münster, Germany
HealthWatch, a UK charity which promotes evidence-based medicine

Please note: This complaint to the ombudsman is not about whether the HPV vaccines do more good than harm. It is about the EMA's conduct, which we believe is an instance of maladministration. It is possible that many of the serious harms that occur after vaccination are autoimmune diseases. However, as we don't know whether these diseases are caused by the HPV vaccines, it must be a research priority to find out. The views we express here and our conclusions are based on the facts we present; they are ours and not those of any organisation.

Contents

Abbreviations	2
Summary of our complaint to the EU ombudsman	3
Outline of the case	6
Our complaint to the EMA over the EMA's handling of the possible serious harms of HPV vaccines	6
Our complaint to the EU ombudsman	8
Experience with the EMA related to two anti-obesity drugs	9
The EMA's general comments	11
The EMA's comments on Brinth's observations	16
Many redactions by the EMA in its documents are not legitimate	33
Uncertainties in the science that were left out of the official report	37
Conflicts of interest	43
Final remarks	54
Appendix. Correspondence related to the declaration of interests for the EMA's executive director	59

Abbreviations

AE: adverse event
CFS: chronic fatigue syndrome
CHMP: Committee for Medicinal Products for Human Use
CRPS: complex regional pain syndrome
DHMA: Danish Health and Medicines Authorities
DoI: declaration of interests
EMA: European Medicines Agency
FDA: Food and Drug Administration
HPV: human papilloma virus
LoQ: list of questions
MAH: marketing authorisation holder
PASS: post-authorisation safety study
POTS: postural orthostatic tachycardia syndrome
PRAC: Pharmacovigilance Risk Assessment Committee
SAE: serious adverse event
SAG: scientific advisory group
UMC: Uppsala Monitoring Centre
WHO: World's Health Organization

Summary of our complaint to the EU ombudsman

On 26 May 2016, we complained to the European Medicines Agency (EMA) over maladministration at the EMA related to safety of the HPV vaccines. The EMA's replies to us did not fully address our concerns. Some of our concerns were not addressed at all, and several of the EMA's statements were either wrong or seriously misleading, or irrelevant for the criticism we had posed. We therefore now complain to the EU ombudsman over the EMA. These are our most important observations:

1. The EMA has not been open and accountable to the citizens and has not respected their rights to know about the scientific uncertainties related to the safety of HPV vaccines. The officially published 40-page report does not reflect the considerable disagreements among the EMA's experts and others but gives the impression of a unanimous rejection of the suspected harms.
2. The EMA has not lived up to the scientific standards that must be expected of the agency when evaluating the science related to the safety of the HPV vaccines. One of the key arguments, which appeared no less than ten times in the EMA's official report, was that there was no difference between what was observed and the expected background incidence of serious harms. However, the underlying research was of such poor quality that these observations are virtually meaningless. The EMA admitted that evidence from observed versus expected analyses cannot confirm a causal association due to the inherent limitations in such data, but then, logically, the EMA cannot provide any reassurance either for the opposite hypothesis, which is that the HPV vaccines are not harmful.
3. Contrary to the EMA's statements, the official report does not describe the most relevant evidence. The EMA emphasized research that is highly unreliable instead of focussing on the most reliable research.
4. The amount of spin generated by EMA on its findings does not allow conclusion to be made. Its official report could have been written by a PR agency working for a drug company. It is of public interest to know who wrote or drafted the EMA's official report, which is anonymous. The bottom line for the EMA seems to have been that the vaccine should be protected from criticism at all costs because it is believed to save lives. One pointer to this is that the text in the official report is nearly identical to the assessments of the EMA's rapporteur and the drug companies.
5. The EMA did not treat a Danish researcher who raised concerns about possible serious harms of the HPV vaccines fairly. The EMA published pejorative comments that came close to an accusation of scientific misconduct. The EMA's comments were unprofessional, totally inappropriate and represented unfounded criticism. If drug regulators behave like this when doctors report their observations about possible serious harms of approved products, doctors will be unlikely to alert the public to their observations in future, which would be a complete negation of one of the cornerstones of pharmacovigilance.
6. The EMA seriously misrepresented the facts when it stated that its co-rapporteurs did not agree with the Danish researcher about her concerns.
7. The EMA did not treat fairly the observations and concerns the Danish Health and Medicines Authorities and the WHO Uppsala Monitoring Centre had raised about possible serious harms of the HPV vaccines.

8. Contrary to the EMA's statements, the evidence was not assessed in an objective and scientifically acceptable way and the evidence provided by experts was not given equal consideration. The evidence provided by the vaccine manufacturers was generally accepted at face value, unlike the more reliable and independent publications by the Danish researcher and her colleagues, the Danish Health and Medicines Agency and the WHO Uppsala Monitoring Centre.

9. The extreme secrecy, with life-long confidentiality agreements, which the EMA imposed on its working group members and scientific experts is not needed, is not legitimate and is not in the public interest.

10. Some of the redactions the EMA imposed on the documents it delivered to the citizens according to Freedom of Information requests were not needed, were not legitimate according to a 2010 ruling by the ombudsman, and were not in the public interest. The illegitimate redactions included names of contact people at the EMA and scientific assessors, case numbers of patients for which harms were reported, country names for individual cases, numbers of reported harms for individual countries, names of countries where there is an excess incidence of reported harms, and number of doses of the vaccine used in individual countries.

11. Some of the experts that participated in the EMA's working groups failed to declare their conflicts of interest, and the EMA's executive director, Guido Rasi, had not declared that he is the inventor of several patents. We believe that, even if the inventor is not the owner of such patents, they should be declared.

12. Contrary to the EMA's statements, the EMA's policy about restricting members of its Scientific Advisory Group meeting to participate fully in the meeting was not correctly applied. For example, there were no restrictions for the chair of the meeting, Andrew Pollard, although he had declared several conflicts of interest in relation to the HPV vaccine manufacturers, while some of the restricted people had no such conflicts of interest.

13. Contrary to the EMA's statements, it is not correct that none of the EMA's scientific committee members and experts had any financial or other interests that could affect their impartiality. The EMA used experts with financial ties to the manufacturers although it is always possible to find experts without such conflicts. The names of some of the experts the EMA consulted were not disclosed.

14. Contrary to the EMA's statements, the review process was not transparent and independent; the collective approach did not minimise the risk of bias; and the information presented by pharmaceutical companies was not scrutinised and independently assessed. Nowhere in an internal 254-page EMA report is there any information that indicates that the data and analyses delivered by the drug companies had been "thoroughly and critically reviewed," the raw data re-analysed or even just checked.

15. The scientific approach to finding possible harms of the HPV vaccines was insufficient. The drug companies' searches for possible harms in their own databases were grossly insufficient, and the search strategies for the companies' and the EMA's searches in the published literature were not revealed, and the EMA even redacted its search strategies. Such redactions make the EMA's work

not replicable and ultimately unaccountable, and may engender suspicion that the searches were scientifically inadequate.

16. Contrary to the EMA's statements, it is not a "very conservative approach" to let the drug companies exclude a large amount of cases diagnosed by a skilled clinician without verifying by inspecting the underlying raw data that this is legitimate. Furthermore, the EMA allowed one-fourth of the vaccine trials to be omitted from the manufacturers' review of the trials for unclear reasons and did not review data from some of the trials in the holdings.

17. We believe it is illegitimate and not in the public interest that the EMA regards the drug companies as the owners of data from clinical trials and data in their safety databases.

18. In all the vaccine trials apart from a small one, the so-called placebo was either not a placebo as it contained aluminium adjuvant, which is neurotoxic in high doses, or it was another vaccine. This makes it difficult to find a difference between harms of the vaccine and the "placebo," but the EMA failed to address this fundamental problem in its official report and allowed the manufacturers to lump all the "placebo" data together. This is contrary to good scientific practice to such a degree that we consider it outright scientific misconduct committed by the EMA.

19. We believe that the EMA's interpretations of the numerous treaties, regulations and rules the agency refers to are partly inconsistent and illegitimate, and not in the public interest.

Outline of the case

Vaccines against the human papilloma virus (HPV) are likely to decrease deaths from cervical cancer, as the incidence of precursors to cancer has decreased markedly after the vaccine was introduced.

In July 2015, the Danish Health and Medicines Authorities (DHMA) asked the European Medicines Agency (EMA) to assess the research that had raised the possibility that the HPV vaccines in rare cases might cause serious neurological harms. Prior to this, Denmark had contacted the European Commission, and the Commission had requested the EMA to give its opinion.

In its submission to the EMA, the DHMA included peer reviewed articles published by PhD and physician Louise Brinth from the Danish Syncope Unit at Frederiksberg Hospital in Copenhagen, which had raised the hypothesis of a link between the vaccine and syncope and other neurological events. The DHMA also included a review of the global data made by the Uppsala Monitoring Centre (UMC, a WHO collaborating centre).

The prominent symptoms, which may be caused by the vaccines, are similar to those seen in so-called functional disorders such as chronic fatigue syndrome (CFS) and they include postural orthostatic tachycardia syndrome (POTS) and chronic regional pain syndrome (CRPS). The prevailing hypothetical mechanism is an autoimmune reaction triggered by either the active component of the vaccine or the adjuvant in the vaccine, or both. The syndromes are difficult to diagnose; their causes are poorly understood; and they are likely to be substantially underreported. This complicates studies of a causal link.

As we believed the EMA's handling of the case constituted maladministration, we submitted a "Complaint to the European Medicines Agency (EMA) over maladministration at the EMA," dated 26 May 2016 (1).

Our complaint to the EMA over the EMA's handling of the possible serious harms of HPV vaccines

On 26 November 2015, the EMA released a 40-page Assessment Report dated 11 November on the safety of the HPV vaccines (2). This is the EMA's official report (2), and it gives the impression of a unanimous rejection of the suspected harms. However, only seven months earlier, the EMA had concluded that, "A causal relationship between the dizziness and fatigue syndrome, Postural Orthostatic Tachycardia Syndrome (POTS) and Gardasil [one of the HPV vaccines] can neither be confirmed nor denied" (3). Moreover, there is an internal EMA report of 256 pages called "Briefing note to experts" (4), which tells a very different story. This report, which provided the draft for the EMA's 40-page official report, is confidential but has been leaked to us in its original form, without any redactions.

There are many problems with the EMA's official report, and one of us, Louise Brinth, drew attention to them in a 63-page document dated 15 December 2015 (5). When she wrote the document, Brinth did not have access to the confidential internal report (4), only to the official one (2). We agreed with Brinth's criticism of the EMA, and our concerns about the EMA's handling of the case increased when we read the internal report. We therefore complained to the EMA over maladministration at the EMA on 26 May 2016.

In our complaint, we highlighted to the agency that according to Article 6 of the EU Treaty and the Charter of Fundamental Rights of the European Union (6):

“Openness enables citizens to participate more closely in the decision-making process and guarantees that the administration enjoys greater legitimacy and is more effective and more accountable to the citizen in a democratic system. Openness contributes to strengthening the principles of democracy and respect for fundamental rights.”

We asked the EMA to assess (1):

A1. Whether the EMA has been open and accountable to the citizens and has respected their rights to know about the uncertainties related to the safety of the HPV vaccines.

A2. Whether the EMA has lived up to the professional and scientific standards that must be expected of the agency to guarantee that the administration enjoys legitimacy when evaluating the science and the data related to the safety of the HPV vaccines.

A3. Whether the EMA has treated fairly - in a manner that guarantees that the administration enjoys legitimacy - a Danish whistleblower, PhD Louise Brinth, when she raised concerns about possible serious harms of the HPV vaccines.

A4. Whether the EMA has treated fairly - in a manner that guarantees that the administration enjoys legitimacy - the observations and concerns the Danish Health and Medicines Authorities and the Uppsala Monitoring Centre had raised about possible serious harms of the HPV vaccines.

A5. Whether the EMA's procedures for evaluating the safety of medical interventions guarantee that the administration enjoys legitimacy. The EMA asked the manufacturers of the vaccines to assess potential harms of their own products in which they have huge financial interests.

A6. Whether the extreme secrecy, with life-long confidentiality agreements, which the EMA imposed on its working group members and scientific experts, is needed; is legitimate; is in the public interest; and guarantees that the administration enjoys legitimacy.

A7. Whether the redactions the EMA imposed on documents it delivered to the citizens according to Freedom of Information requests were needed; were legitimate; are in the public interest; and guarantees that the administration enjoys legitimacy.

A8. Whether the EMA has behaved in a manner that guarantees that the administration enjoys legitimacy in relation to declaring conflicts of interest. We noticed a Guido Rasi's name associated with patents for inventions and wonder whether this is the same person who is the EMA's director. If so, we believe Rasi has failed to declare his conflicts of interest. We also believe that the rapporteur for the EMA's report, Julie Williams (2), has failed to declare her conflicts of interest.

A9. Whether the EMA behaves in a manner that guarantees that the administration enjoys legitimacy when the agency use experts with financial ties to the manufacturers, in particular considering that it is always possible to find experts without such conflicts.

A10. In the interest of transparency, we urge the EMA to ensure that the names of all the experts consulted are disclosed together with their conflict of interest declarations. We also urge the EMA to ensure that the conflicts of interest statements from the rapporteur, the co-rapporteurs (Jean-Michel Dogne (BE) and Qun-Ying Vue (SE)), their contact persons at the EMA and everyone else who has given statements to the EMA are brought out in the open. Finally, we urge the EMA to ensure that Declarations of Interests for officials at the EMA are honest.”

The replies we received from the EMA came in three parts:

On 17 June, Noël Wathion, EMA’s Deputy Executive Director, addressed conflicts of interest issues related to Guido Rasi in a 2-page letter to Peter C Gøtzsche, which, among other things, stated: “The Agency’s Executive Director Prof Rasi is indeed mentioned on a number of patents, even beyond those referred to in footnote 15 of your complaint letter, but only as inventor, not as owner of the patents” (7).

On 1 July, Noël Wathion sent the EMA’s response (17 pages) to the other issues we had raised, also addressed to Peter C Gøtzsche only (8).

On 8 July, Carter-Ruck solicitors in London sent a 5-page letter, also addressed to Peter C Gøtzsche only, marked “Private and confidential” on behalf of their client, Guido Rasi (9). According to this letter, Rasi hoped that “you will agree immediately to amend the relevant passages of the Publication [our complaint over the EMA], and to publish (in terms to be agreed) a suitable statement of correction and apology withdrawing these false allegations.” This letter led to a long correspondence, which we have reproduced in the Appendix, as we feel it has general interest.

Our complaint to the EU ombudsman

The EMA’s replies to us did not fully address our concerns. Some of our concerns were not addressed at all, and several of the EMA’s statements were either wrong or seriously misleading, or irrelevant for the criticism we had posed. We therefore complain to the European ombudsman as we still believe the EMA’s handling of the HPV vaccines case is an instance of maladministration.

In its main reply to us (8), the EMA justified its decisions with reference to many regulations, rules, guidelines and opinions. We don’t have confidence that the agency has interpreted these documents in a way that ensures openness, gives the administration legitimacy, makes it accountable to the citizens, and respects fundamental rights of access to information that is important for the citizens when they make decisions about healthcare, as outlined in Article 6 of the EU Treaty and the Charter of Fundamental Rights of the European Union (see above) (6).

The reason why we don’t have confidence in the way the EMA interprets and uses the rules is especially - but not only - related to Regulation (EC) No 1049/2001 (6), which the EMA mentions six times in its document to justify its actions. According to this regulation, a basic principle in the European Union is to allow its citizens the widest possible access to the documents its agencies possess. However, based on our previous experience with the EMA, we don’t have any confidence in the way the EMA interprets this particular regulation. As this regulation is very important, we shall explain in some detail what we experienced previously, which we described in the British Medical Journal in 2011 (10). We believe that the EMA’s arguments in our earlier case are of considerable

interest and relevance for the current case, which is also about possible serious harms of a medical intervention.

Experience with the EMA related to two anti-obesity drugs

In 2007, researchers at the Nordic Cochrane Centre applied for access to the clinical study reports and corresponding protocols for 15 placebo controlled trials of two anti-obesity drugs, rimonabant and orlistat, which the manufacturers had submitted to the EMA to obtain marketing approval in the European Union (10). The researchers explained that secrecy was not in the best interests of the patients because biased reporting of drug trials is common and that they hadn't found any information that could compromise commercial interests in 44 trial protocols of industry initiated trials they had reviewed previously.

Without any comment on the researchers' arguments, the EMA replied that the documents could not be released because it would undermine commercial interests. The researchers appealed to the EMA's then executive director, Thomas Lönngrén, and asked him to explain why the EMA considered that the commercial interests of the drug industry should over-ride the welfare of patients. The researchers argued that the EMA's attitude increased the risk of patients dying because their doctors prescribed drugs for them without knowing what the true benefits and harms were. Lönngrén ignored their request for clarification and told them they could lodge a complaint with the European ombudsman, which they did.

Over the following three years the EMA put forward several arguments to avoid disclosing the documents: protection of commercial interests, no over-riding public interest, the administrative burden involved, or the worthlessness of the data to the researchers after the EMA had redacted them. The agency seemed not only to deliberately avoid allowing the researchers access with four invalid arguments, but also to deliberately protract the process, as it did not respond to the ombudsman's letters before his rather generous deadlines had run out.

Protection of commercial interests was the EMA's over-riding argument, but the agency seriously misrepresented the facts, e.g. when it declared that it would undermine the protection of commercial interests to allow access because the documents represented the full details of the clinical development programme. There are no such details in these documents.

The researchers explained, among other things, that the clinical study reports and protocols are based on well-known principles that can be applied to any drug trial; that the clinical study reports describe the clinical effects of drugs; and that nothing in the EMA's guidelines for preparation of such reports indicates that any information included in them can be considered a trade secret. The trial protocols are always sent to the clinical investigators, and it is unlikely that companies would have left in any information that could be of commercial value.

The European ombudsman, P Nikiforos Diamandouros, noted that the risk of an interest being undermined must be reasonably foreseeable and not purely hypothetical. He could not see that access would "specifically and actually" undermine commercial interests. He inspected the relevant reports and protocols at the EMA and concluded that the documents did not contain commercially confidential information, in accordance with the researchers' observations. He therefore criticised the EMA's refusal to grant them access.

Even if commercial interests were undermined by disclosure, access would still have to be granted if there was an over-riding public interest, which the researchers had argued was clearly the case. Anti-obesity pills are highly controversial. The effect on weight loss is small, and the harms are substantial. People have died from cardiac and pulmonary complications or have experienced psychiatric disturbances, including suicidal events, and most of the drugs have been deregistered for safety reasons.

Despite the researchers' convincing arguments, the EMA replied that it could not identify any over-riding public interest and remarked that the evaluation of safety and efficacy of drugs is its responsibility. This argument was completely off topic, which was about whether the citizens should have the possibility of seeing the facts for themselves and make up their own minds about the drugs. There are countless examples where drug agencies have been far too slow to react to signals of serious harm, and this relaxed attitude to drug safety has led to tens of thousands of deaths that could have been avoided (11).

The ombudsman indicated that the researchers had established an over-riding public interest, but he did not take a definitive stance on whether an over-riding public interest existed because this question needed answering only if disclosure undermined commercial interests. He asked the EMA to justify its position that there wasn't an over-riding public interest, but the EMA avoided replying by saying that the researchers had not given evidence of the existence of such an interest, although they had done that. Furthermore, the EMA's argument was irrelevant. A suspect asked for his alibi on the day of the crime doesn't get off the hook by asking for someone else's alibi.

The EMA's other arguments were also invalid. According to the EMA, the redaction of (unspecified) "personal data" would cause the EMA a disproportionate effort that would divert attention from its core business, as it would mean redacting 300,000-400,000 pages. In contrast, the Danish Drug Agency had not seen the workload as a problem when it granted the researchers access to the reports for a third anti-obesity drug, sibutramine, which was locally approved in Denmark (this drug was taken off the market in 2010 for safety reasons). The 56 study reports the researchers received comprised 14,309 pages in total, and in comparison, they requested only 15 study reports from the EMA. If the EMA's statement was not a lie, it came very close. It was totally impossible that 15 study reports and its protocols could take up 300,000-400,000 pages. Rimonabant (Acomplia) was never approved in the United States because of its serious harms, and its approval in Europe was withdrawn by the European Commission on 16 January 2009 during the researchers' complaint proceedings with the ombudsman. When they ultimately received the reports they had requested for the only remaining anti-obesity drug on the market, orlistat, there were only 7 trials and the total amount of documentation was only 8,716 pages (12).

Of relevance for the HPV case is also the EMA's argument that, "as a result of the redaction exercise, the documents will be deprived of all the relevant information and the remaining parts of them will be worthless for the interest of the complainant." From what the researchers knew of clinical trial reports and protocols it struck them as odd that they would contain so much "personal data" that the documents became worthless. In contrast:

The ombudsman noted that the requested documents do not identify patients by name but by their identification and test centre numbers, and he concluded that the only personal data are those

identifying the study authors and principal investigators and to redact this information would be quick and easy.

The EMA was completely resistant to the researchers' arguments and those from the ombudsman. However, after the ombudsman accused the EMA of maladministration in a press release on 7 June 2010 (13), three years after the request, the EMA reversed its stance. The EMA now gave the misleading impression that it had favoured disclosure all the time, agreed with the ombudsman's reasoning, and noted that the same principles would be applied for future requests for access but that it would consider the need to redact part of the documents.

The researchers received the data they requested from the EMA on 1 February 2011, which in some cases included individual patient data in anonymised format, identified by individual and test centre numbers.

The researchers concluded in their published paper about this affair (10) that, according to the EMA's responses to the ombudsman, the EMA put protecting the profits of the drug companies ahead of protecting the lives and welfare of patients. They also noted that if the knowledge base is incomplete, patients may suffer and cannot give fully informed consent when asked to participate in trials, and that the EMA should be promoting access to full information that will aid rational decision making, not impede it.

After his efforts at protecting the industry's commercial interests, the EMA's executive director, Thomas Lönngren, quit the EMA. Although Lönngren had been told by the EMA that he should not provide product-related advice to drug companies or take managerial, executive or consultative positions in the industry for a period of 2 years, he became director of a new company, Pharma Executive Consulting Ltd, in November 2010 while still employed by the EMA (14).

The EMA's general comments

The EMA's main letter to us (8) started with general comments, which we have numbered below for ease of cross-referencing in the remainder of the text.

B1. The EMA noted: "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" (8, p1).

In our view, this is an irrelevant remark. Our complaint is not about whether the vaccines do more good than harm, or whether they cause the alleged harms, but about the EMA's conduct. Furthermore, the EMA makes an undue and erroneous assumption, just like it did about Brinth (see item C1 below). Needless to say, none of us have changed our approach to science and we do not overestimate the value of studies that have no control group. The limitations of randomised trials for assessing rare harms, and the necessity for observational studies in this context, are well-known in the scientific community. It is inappropriate for an EU agency to make such assumptions about people who criticise them. The EMA should stick to the facts and should not engage in guess-work.

B2. The EMA's statement that, "the use of HPV vaccines is expected to prevent many cases of cervical cancer" is also irrelevant for our complaint, but it says something important about the EMA. This is exactly how the drug industry argues: don't worry about the harms, as our drugs prevent many deaths.

B3. The EMA stated that the review process is transparent and independent; that the collective approach minimises the risk of bias (p1); and that "stringent legal and regulatory safeguards are in place to ensure that any information presented by pharmaceutical companies is scrutinised and independently assessed" (p2).

We do not agree that the information presented by pharmaceutical companies was scrutinised and independently assessed; it was generally taken at face value. The assessors based their judgements on aggregate data provided by the manufacturers; they did not check the manufacturers' results, verify the appropriateness of excluding reports of suspected harms, carry out independent analyses, or access the raw data of the trial datasets presented in the responses by the manufacturers (15). There is no trace of re-analyses in the documentation. This is a fundamental failure, as the companies have a huge vested interest in NOT finding the possible harms in their databases, and as we assume the EMA knows that drug companies should not be trusted (11,16).

We also believe that the collective approach was not one that "minimises the risk of bias." If anything, consensus committees increase the risk of bias, as they often have one or two dominant people with strong views. In fact, according to information available to us, those who expressed concerns about vaccine safety at the Scientific Advisory Group (SAG) meeting on 21 October 2015 were pressurised by the leaders to agree to the so-called consensus. That is not science but politics. We will return to this problem under item C5.2 below.

B4. "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" (p2).

We find that the evidence was not assessed in an objective and scientifically acceptable way, and it was not given equal consideration. For example, the co-rapporteurs were overruled by the rapporteur and their divergent opinions were left out of the official report (4). The data provided by the marketing authorisation holders (MAHs) were generally taken at face value, in contrast to the much more reliable independent research carried out by Brinth. There were also subjective, unfounded and erroneous allegations about Brinth's research whereas the limitations of the randomised trials related to detection of rare events and the use of active substances as "placebo," were not taken into account (see items C1 and C9 below).

B5. "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" (p2).

It is misleading to say that the official report describes the most relevant evidence. The EMA's confidential report of 256 pages (4) tells a story about uncertainty related to whether the HPV

vaccines can cause serious harms, and it also contains serious criticism of the EMA's procedures and the conclusions made, by both the co-rapporteurs, other experts and the DHMA. Relevant evidence in support of the criticisms was not included in the official report (see below). In contrast, the official report sends the message that "everybody agrees that there is nothing to worry about," which is also exactly how the Danish media interpreted the EMA's report. The same day the EMA's report came out, a major Danish newspaper brought the headline: "Danish researchers demolished: no relation between the HPV vaccine and serious symptoms," and the article even insinuated that Brinth and her group had committed scientific misconduct (17).

We believe the public has a fundamental right to know that there are uncertainties, which can be important for their decisions about medical interventions, and that the EMA through its inappropriate actions, rather than protecting the whistleblowers that raised a suspicion of serious harms caused by the vaccine, ignited a public witch hunt on the Danish researchers. Hiding disagreement and uncertainty about harms of the vaccine may fuel distrust rather than foster it.

B6. "EMA makes all available information that its [sic] 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."

It seems to us that the EMA has "forgotten" the ombudsman's ruling in our previous case. The ombudsman remarked in 2010 that since the requested documents did not identify patients by name but by their identification and test centre numbers, the only personal data to redact were those identifying the study authors and principal investigators (10). However, as we explain below (under items D1 to D8), the EMA redacted far more than this in the HPV case.

B7. "EMA's approach to conflicts of interests [sic] is a balanced approach aiming to effectively restrict the involvement of experts with possible conflicts of interests [sic] 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."

We believe this is not correct. Among the core members of the SAG were Margareta Blennow and Anders Lindberg who appeared on the list of SAG members we received from the EMA on 9 June 2016 (18), but we could not find any conflicts of interest declarations for these two people on the EMA's website when we checked it in May 2016. See further discussion of this issue under item F2 below.

B8. "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."

This statement is misleading. In the EMA's 256-page internal report (4), there is a "**Confidentiality Reminder**" on page 2:

“As an EMA expert you are bound to life-long duty of confidentiality. The duty of confidentiality applies to all information of the kind covered by the obligation of professional secrecy. This includes, for example, the fact that there is a meeting, that you have been nominated to participate, the agenda of the meeting, the product or company concerned, the participants, any part of the discussions and outcome. All documentation (correspondence, reports, minutes, etc.) must be kept as confidential and stored in a secure place or destroyed. The duty of confidentiality stops only if information has been made public and only to the extent that has been released into the public domain.”

This is not a permission to discuss disagreements in public; it amounts to a gagging clause. According to information we have, the members of one of the EMA’s committees clearly felt that this amounted to a life-long prohibition to speak in public about disagreements. We have also been told that a person who posed critical questions was reminded of the life-long confidentiality. Furthermore, the EMA’s misleading post hoc statement has a safeguard. People are not allowed to disclose commercially confidential information, but since the EMA, just as the drug industry, defines what they mean by “commercially confidential information”, which changes over time (10,19), we doubt that anyone would dare speak out in public even now, after the EMA’s post hoc statement. How would these experts know what the EMA currently considers confidential?

B9. “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.”

This is not correct. As explained above, the EMA did everything it could to prevent us from getting access to the clinical study reports on two anti-obesity drugs in its possession until it was forced by the ombudsman to reverse its stance in 2010 (10). Further, after 2010, the EMA has tried to wind the clock back to its culture of extreme secrecy. In the AbbVie case, the EMA redacted much information in 2014 that, in the ombudsman’s opinion, did not require redacting, e.g. the rationale for dosage selections; the considerations used in determining sample sizes for clinical trials; and text relating to protocol changes (19). Prior to this, in the spring of 2013, AbbVie had dragged the EMA into the European Court because of its new openness policy, and at a meeting in Brussels later the same year, AbbVie incensed European drug regulators by making it clear that it regarded clinical trial data on adverse events as confidential information that it was entitled to keep to itself (20).

In 2014, the EMA suggested a “peeping Tom” policy. No one would be allowed to download redacted reports, and they could be viewed on screen only (taking photos of the screen pictures would also be prohibited, according to information we received at a meeting at the EMA back then); some statistical analyses could be commercially confidential; safety and efficacy data about off-label prescribed drugs could be kept out of third party view; researchers would have to contractually agree that third parties (i.e. pharmaceutical companies) would have direct legal claims under UK law against them for possible violations of the Terms of Use; infractions to the cumbersome procedural limits could thus not only be punished by withdrawal of access but appeared also to open up the possibility of spurious lawsuits over “misuse of data” that essentially would silence critics (21). The EMA’s 2014 proposals would have made relevant research about drug safety virtually impossible and they caused a public outcry including a protest from the EU’s ombudsman (22). In two responses, the EMA’s executive director Guido Rasi defended the agency’s draft policy, explaining that the EMA’s

latest draft policy represented “absolutely no change in direction.” It surely did, and the EMA had to backpedal (22).

B10. “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” (p3).

The EMA is far from being an agency that is “open and accountable to EU citizens” and the EMA’s reply to our complaint did not increase our confidence in the agency.

B11. “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 ... 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” (p4).

“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 Vaccines was convened, which is a standing group of leading experts in the field of vaccines and vaccine safety. It was created in 2012 ... 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” (pp4-5).

“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” (p5).

“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.”

We have several concerns with this. The (Co)-Rapporteurs are crucial for the validity of the whole scientific process as they are those who “take the lead in the scientific assessment and who have the task of thoroughly assessing the data and draft their recommendations.” As they are the ones who know best, it is concerning that they were consistently overruled by the Rapporteur when she had another opinion, which invariably favoured the view that the suspected harms were not related to the vaccine (4). It is also concerning that in an area with so much uncertainty, “The PRAC reached its scientific recommendation by consensus following plenary discussion.” It is very common in group work that one or two people dominate the process and that its outcome may therefore reflect more what these 1-2 people think than the disagreeing views that existed in the group (see our note about

the leaders pressurising those who expressed concerns about vaccine safety under item B3 above). Science is the antithesis of “consensus,” and scientists did not arrive at the laws of nature by a consensus process.

We are also concerned that the consensus “recommendation was presented in the final PRAC assessment report which summarised all the data assessed by the committee in support of the PRAC conclusions.” This looks like cherry-picking. What about all the data and evidence-based criticism that did NOT support the PRAC conclusions (see our comment under item B5 above)? Apparently, if we compare the internal report with the published report, the relevant criticisms seem to have disappeared. Our final concern is that, although the (Co)-Rapporteurs were supposed to thoroughly assess the data, they didn’t do this. They accepted most of what they got from the drug companies at face value (see items B3 and B4 above).

“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” (p5).

As noted under items D1 to D8 above, some documents are so extensively redacted that they may be useless for certain research purposes.

The EMA’s comments on Brinth’s observations

We use below the same numbering as we used in our complaint to the EMA over the EMA (1).

C1. The EMA asserted in its published report (2, p24) that: “Overall, the case series reported by Brinth and colleagues (2015) is considered to represent a highly selected sample of patients, apparently chosen to fit a pre-specified hypothesis of vaccine-induced injury.” In our complaint to the EMA (1), we noted that Brinth stated in her report (5, p17) that she and her co-workers included all consecutively referred patients, with the exception of those that met the exclusion criteria. We found that the EMA’s allegations constitute guesswork (“apparently”), are pejorative and come close to an accusation of scientific misconduct. We furthermore noted that the EMA’s comments are totally inappropriate for an EU authority to make on honest researchers and that the EMA’s criticism was totally unfounded.

In its reply, the EMA explained that “the methodology of case series has important limitations as it lacks a comparator group and is also known to be vulnerable to selection bias ... 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” (pp5-6).

The EMA is evasive. Its discussion about bias is irrelevant and it is clear from Brinth’s research that she was aware of this risk and had pointed out the well-known limitations of the research design. Further, it is NOT an objective consideration to say about a researcher that she used a “highly

selected sample of patients, apparently chosen to fit a pre-specified hypothesis of vaccine-induced injury.” Brinth felt that this comment was defamatory.

C2. The EMA asserted in its published report (2, p23) that, “many of these symptoms would require some sort of objective clinical evaluation, yet there is no information on how this was done or what other clinical assessment may have been undertaken to exclude other causes of the symptoms.” Brinth noted that nausea, headache, abdominal pain and fatigue are subjective symptoms that escape “objective clinical evaluation,” and that orthostatic intolerance was quantified through tilt-testing, which constitutes more than “some sort of objective clinical evaluation.” Brinth furthermore noted that the evaluation of her work as presented by the EMA in its official report is based on many assumptions, most of which she believed were wrong. She was also concerned that the EMA report did not include the complete data set, and that it was not defined how the included parts were chosen. She found that this had resulted in several inconsistencies between the representation of the Uppsala Monitoring Centre (UMC) data in the original DHMA report and the EMA report (5, pp25-26). Brinth furthermore noted that her observations and hypotheses were supported by the independent review of the global data made by the UMC (5, p26).

In our complaint to the EMA, we noted that we found that the EMA’s comments about Brinth’s research were unprofessional, misleading, inappropriate and pejorative, and that the EMA’s approach involved cherry-picking, which is unscientific. We noted that the Uppsala centre had received more reports of potential harms from the HPV vaccines than reports of similar harms from all other vaccines offered to women. We also noted that although both EMA reports mentioned the finding by the UMC that a substantially higher proportion of case reports were classified as serious for the HPV vaccines compared to other vaccines, no attention was paid to this in either of the EMA reports (2,4).

In its reply to us (p6), the EMA noted that the imbalance in the absolute numbers of reports of POTS/CRPS with HPV versus non-HPV vaccines was not statistically significant. We cannot comment on this, as we have not seen the statistical analyses. However, we find it relevant to reiterate that the EMA paid no attention to the fact that the cases were more serious for the HPV vaccines than for other vaccines. We also note that Brinth wrote that there were a number of important and relevant, potential side effects, which were statistically significantly over-reported with the HPV vaccine, but which the EMA failed to mention: disturbances in consciousness, muscular weakness, disability issues, and neurological signs and symptoms (5, p29).

We have discussed these issues with key people at the UMC, Ralph Edwards and Rebecca Chandler. They considered that their data were disregarded much too easily by the EMA and without adequate justification, given that it meant ignoring a large number of seriously affected patients with prolonged significant disability and admission to hospital from consideration of whether serious harm is caused by the vaccine, even at the hypothesis stage. They regard the EMA report as inadequate and worryingly dismissive. They have now published a paper with more data and arguments that strengthen their suspicion that the HPV vaccines may cause serious harms (23). They reported that the combination of headache and dizziness with either fatigue or syncope was found to be more commonly reported in HPV vaccine reports compared with non-HPV vaccine reports for females aged 9-25 years. This disproportionality remained when those countries reporting the signals of CRPS (Japan) and POTS (Denmark) were excluded.

C3. The EMA asserted in its published report (2, p27) that the chronic fatigue syndrome has “been reported relatively constantly since 2009.” Brinth noted that, according to the UMC report, the chronic fatigue syndrome has “been increasing since 2012 with a marked increase between 2012 and 2013” (5, p27). In our complaint to the EMA, we noted that we believed that the EMA had misrepresented the UMC report with regard to possible serious harms of the vaccine.

In its reply (p6), the EMA stated that it may have been misunderstood and that “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.”

However, the text in the EMA’s published report was: “Fibromyalgia, CFS and ME/PVFS have been reported relatively constantly since 2009 (with a slight decrease in 2011/12), but reports of POTS and CRPS had notably increased since 2013.” The EMA misrepresented these facts in its reply to us. Firstly, although using quotation marks, the EMA provided a misquotation when it left out “relatively” and “(with a slight decrease in 2011/12).” Secondly, and more important, a text that says that something has increased, and then decreased, and that something else has been reported relatively constantly, cannot be misunderstood.

C4. The EMA failed to mention not only that the Danish reports were more often classified as “serious” but also that they had more often included a large amount of clinical, relevant information than reports from other countries. Instead, the EMA mentioned that “the terms POTS, orthostatic intolerance and autonomic nervous system imbalance are reported disproportionately more in HPV reports from Denmark vs HPV reports in other countries” (2, p27). Brinth drew attention to the fact that the UMC had noted that a significantly greater proportion of the reports from Denmark were considered “good reports;” were classified as “serious;” and were received from either a physician, a consumer or a lawyer (5, p28).

We found that the EMA, rather than praising the Danish diligence, cast doubts on whether the Danish peer reviewed research should be believed. We noted that this is an inappropriate attitude to safety for a drug agency to have and that we agreed with Brinth that the EMA had misrepresented the UMC review in its own report, thereby creating the impression that Brinth should have published substandard research. The EMA had furthermore omitted some of the important suspected harms of the vaccine.

In its reply (p6), the EMA stated: “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.”

We find the EMA’s reply highly misleading. It is not a “very conservative approach” to let the drug companies exclude a large amount of cases diagnosed by a skilled clinician without verifying by inspecting the underlying raw data that this is legitimate, see item C7 below.

C5. Brinth had the impression that the minutes from the EMA meetings were not released and might not be publicly accessible either, and she found it unclear which data people reviewed at the meetings. She also criticised the EMA’s published report for giving the impression that all the experts had agreed, which she called a false consensus based on the participants being bound to secrecy, particularly as she did not believe that two single scientists would share exactly the same views in a matter as complex as this. She found it “a very strange, unscientific and undemocratic approach” (5, p33).

We informed the EMA that we agreed with Brinth and that the EMA’s official 40-page report (2) is misleading, as it gives people the impression that there is nothing to worry about in relation to vaccine safety and that the experts consulted by the EMA agreed on this. We also noted that the EMA’s confidential, internal report (4) revealed that several experts were uncertain and called for further research, but that there was nothing about this in the official report. Finally, we noted that the extreme level of secrecy - life-long - imposed by the EMA on its working group members and other experts was inappropriate and went against the public interest in openness and transparency about possible serious harms of the vaccine.

The EMA’s reply to us on this point was very long, and we have therefore divided it up in seven parts.

C5.1. The EMA stated that, “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” (p7).

This is not transparent. Does the phrase “The SAG does not release any minutes document after its meeting” mean that minutes are not taken? Or does it mean that minutes were taken but not released, in which case it is relevant to know whether they are confidential or whether the public can get access to them. We asked the EMA about the minutes and received 6 pages labelled “Confidential” (24) where several names had been redacted (see item D7 below).

C5.2. The EMA stated that, “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.”

This statement documents that even though the EMA involved a scientific advisory group (SAG), the EMA does not focus on science but on politics. When people sit in a room together and know that it

is expected of them that they reach consensus, it is not surprising that consensus is actually reached. Those who have differing views will feel a pressure to agree with the majority, and it is well-known from countless studies in psychology that such group pressure and group think can make people agree to things that directly contrasts with what they actually think about the subject. Science is about encouraging people to air their different interpretations of the data openly, as this is how science is best advanced; it is the very heart of science. In our view, the EMA's processes, which lead to secrecy about differing views, mean that the EMA does not enjoy legitimacy. As the EMA's most important work is to assess the benefits and harms of drugs, it is to be regarded as a scientific institution. The EMA is NOT a policy setting body, but that is how it behaves.

C5.3. The EMA noted: "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.'*"

The EMA consistently quotes Article 4 of Regulation (EC) No 1049/2001 when they talk about NOT giving the public full access to documents. It seems to us that the EMA has chosen to ignore what this regulation is about. It is NOT about introducing secrecy and obstacles, in fact quite the opposite. It is about openness, and according to this regulation, a basic principle in the European Union is to allow its citizens the widest possible access to the documents its agencies possess. If the 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. The EMA could even have made all the documents easy to download, perhaps after redaction of a few names, which would have been quick and easy to do (10). Instead, the EMA did the opposite. It is not possible for citizens to request documents when they have no idea about which documents exist, and it requires immense detective work to try to find this out. The life-long obligation to secrecy in relation to the EMA's scientific meetings contrasts sharply with the practice at its US counterpart, the Food and Drug Administration, where such meetings are open to the public and sometimes available by webcast.

C5.4. The EMA stated: "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."

We feel that this is not an explanation but an evasive statement. The EMA could - and should - have concluded that more research was needed because of the current uncertainty. This has nothing to do with recommending any particular institution or authority to do such research.

C5.5. “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.”

We find that the EMA’s explanation above is in direct contrast with what the EMA stated earlier in their reply to us, namely that “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” (see item B8 above). We also fail to understand what the difference should be between “life-long confidentiality” and “life-long secrecy” and the EMA does not explain why it distinguishes between the two. We furthermore wonder how it is possible for the EMA to issue two contrasting explanations that seem impossible to reconcile.

C5.6. The EMA noted: “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)” (p8).

The EMA’s mentioning of numerous treaties, regulations and rules cannot justify that the EMA is inconsistent when it interprets them. The EMA cannot have life-long secrecy and freedom for its experts to speak out at the same time.

C5.7. The EMA stated: “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.’*”

This is certainly not how the experts interpreted the gagging clause they were presented with on page 2 of the 256-page internal document (see the text under item B8 above). If the EMA really meant what they wrote, then why then did the EMA not tell its experts that this was the case? Why wasn’t this important information made explicit in the rules for the committees?

C6. In her “responsum,” Brinth noted: “Reading EMA’s report it seems to me that the review of the safety data which includes available data from the clinical trials and post-marketing surveillance and

the literature review was all collected by the marketing authorization holders (MAHs) [GlaxoSmithKline Biologicals, Merck Sharp & Dohme Limited, and Sanofi Pasteur MSD]? This must have been in the form of a report written by the MAHs to the EMA? Is this report freely available?" (5, p34).

We wrote to the EMA that we found it "unacceptable that the EMA in its official report (2) did not make it clear that it allowed the drug companies to be their own judges (4) when evaluating whether the vaccine is safe, particularly since there is a huge amount of money at stake: The global expenditure so far on HPV vaccines can be roughly estimated at €25 billion. The EMA asked the companies to search for side effects of the vaccine in their own databases and did not check the companies' work for accuracy. This is not an acceptable procedure. There are countless examples of drug companies hiding serious - even lethal - harms from the authorities (6) [not the current reference 6]."

The EMA replied that, "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" (p8).

We disagree with the EMA's statement that the drug companies are the owners of clinical trial data and the ombudsman also seemed to disagree when he, in 2010, called it maladministration that the EMA would not give us access to such data (10). The statement tells us that the EMA is primarily concerned with protecting the drug companies' commercial interests rather than protecting the patients. There was no doubt about this when Thomas Lönngren was the EMA's executive director (10), and there seems to be little doubt about it today when Guido Rasi is the executive director. Patients run an unknown risk by volunteering to participate in clinical trials, and without this altruism and sacrifice for the common good, there would be no drug trials. Therefore, clinical trial data belong to the patients, in fact to every one of us. The drug companies have caused tremendous harms by withholding trial data, arguing that they are their property and commercially confidential. The withholding of trial data has resulted in millions of patients losing their lives unnecessarily because their doctors did not know how dangerous the drugs were that they prescribed to them, and it is a major reason that our prescription drugs are one of the leading causes of death, after heart disease and cancer (11,16).

The EMA cannot protect the drug companies' commercial interests and the patients against drug harms at the same time. Currently, we consider the EMA dysfunctional and lacking legitimacy when it states that the drug companies are the owners of clinical trial data. It is about time that the agency sided with patients.

As we have stated above under items B3 and B4, the companies' analyses and interpretations seem to have been taken mostly at face value, which is not a scientific approach. The EMA stated that, "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.” We find this statement misleading in relation to the HPV case, as few questions were asked (4; search for “Assessor’s comment”) and as the (Co)-Rapporteurs did not seem to have assessed the data, but simply believed them. Throughout the whole document where the EMA provides replies to our complaint over the EMA, the EMA refers to procedures and tells us what *might* have happened according to these procedures. We also find this misleading. We made concrete observations in our complaint to the EMA but instead of replying in a similarly concrete way, the EMA doesn’t tell us what actually happened, only what ideally *might* have happened. This is not openness and it is not the type of argument that would be allowed in a court case. A person who has broken the law will not get off the hook by saying that according to the law it is not allowed to break the law.

The EMA also stated: “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” (p8).

We shall comment on the EMA’s and the MAHs’ literature searches under item C11 below.

C7. Brinth found it highly problematic that readers of the EMA reports – and particularly herself in her capacity of a medical professional having diagnosed and evaluated a substantial part of the Danish cases – did not have access to the EMA’s case detection methods. Since a substantial proportion of the POTS cases reported as suspected side effects from Denmark had been examined by her, she found it troubling and strange to see that POTS cases had been overruled by MAHs/EMA and judged as not meeting or only partially meeting the diagnostic criteria in 50 out of 83 cases given the diagnosis POTS in the Adverse Events Reports (AERs). She interpreted the EMA’s published report (2) as meaning that it was the MAHs that had evaluated the AERs and noted that she and her co-workers had used the exact same criteria as those mentioned in the EMA’s report when they diagnosed POTS, and that they had been quite restrictive in their diagnostic practice. Brinth wanted to know whether the MAHs had based their evaluation on the AERs alone, or whether they had been through the whole medical record for these patients. She noted that it is well known that an AER will not include all the details of the clinical history and that it is therefore rare that any spontaneous report will meet the diagnostic criteria. She also noted that the WHO (the Uppsala Monitoring Centre) had stated that the Danish AERs did not in the essence differ from reports from the rest of world – but were of a higher quality (5, pp34-35).

We wrote to the EMA stating that we found it unacceptable that no one - not even the person whose research was so strongly (and unfairly) criticised in the EMA’s official report (2) - can judge on what grounds and by whom 50 out of 83 cases of POTS were dismissed by the EMA. We also noted that the secret internal EMA report (4) revealed that the POTS cases were dismissed *without* having access to the full medical records; that the “research” carried out by the drug companies clearly did not live up to accepted standards for such research; and that the EMA did not ensure that it did. We found this very serious because the EMA used the companies’ assessments to overrule the research done by Brinth, which is of a much higher standard and publicly available.

We furthermore noted to the EMA, with reference to the PRAC co-rapporteur's referral updated assessment report (25, pp9-10) that the Danish Health and Medicines Authorities (DHMA) had also strongly criticised the EMA's approach: "The main conclusion in the Danish report is not, as described in the assessment, to change focus to CFS. Rather the review highlights the necessity to evaluate combinations of symptoms rather than only performing separate evaluations of individual diagnoses. It shows that although the number of POTS cases is very high in Denmark, compared to the rest of the world, the symptom pattern seen in the Danish dataset is similar to reports submitted from other countries. Even though it cannot be shown for certain at this point, it is likely based on these data, that patients with the same symptomatology would receive different diagnoses in different member states e.g. POTS in DK and CFS/ME in others. This consideration is important for the discussion of consistency regarding the POTS signal, where it is stated that the finding of the majority of POTS cases in Denmark does not support a causal relationship. We do not agree with this conclusion based on the data."

Immediately after this, the DHMA stated under Risk Management Plan/ Post-authorisation Safety Studies/ Conditions: "Need for further studies regarding the signal for POTS: We agree with the conclusion from the rapporteurs and also state in the Danish report [this shows that these comments come from the DHMA], that the data from spontaneous reports cannot be used to provide evidence for a causal relationship between symptoms and vaccination. However in view of the methodological limitations of the data available and the fact that the observed cases did exceed the expected cases, especially in Japan and Denmark, the conclusions should be cautious and the signal cannot be dismissed either based on the current evidence. We recommend that the vaccine SAG and expert meeting include a discussion of the need and possibilities to design appropriate PASS studies [post-authorisation safety studies] to explore POTS further. Similar question as Q3 regarding CRPS."

In their reply to us, the EMA stated: "All PRAC members had the opportunity to comment in writing during the commenting phase ... 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" (p8).

Again, the EMA avoided answering our serious concerns. The EMA describes what *might* have happened according to the rules, but not what *did* happen, which may have been very little or nothing. We have found no data, for example, suggesting that any important questions were asked to the drug companies at the SAG meeting.

The EMA also wrote: "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" (p9).

This "explanation" is meaningless. Considering the considerable disagreements that existed at all levels in this process, not least the serious criticism from the DHMA (only available in the EMA's internal report (4)) that originally raised the concerns about possible serious harms of the HPV vaccines and asked the EMA to look into this, we wonder why nothing about these disagreements

was made public. We also note the strong hold the EMA has on the consensus committee. People are not likely to express disagreement with the majority, as they would then be exposed publicly. It is much easier to swallow what comes on the table, even if you disagree with it. But this is the opposite of science. What came out of this meeting, we would call a cosmetic consensus.

The EMA wrote to us: “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).”

The fact that 50 out of 83 cases of POTS were dismissed by the MAHs and subsequently also by the EMA (see just above, under this item) shows beyond any doubt that neither the MAHs, nor the EMA, did their work properly.

C8. Brinth wrote that the EMA's official report noted on page 12 that PRAC requested the MAHs to search not only “for reports specifically containing the terms POTS and CRPS” but also to use “common search strategies” to identify possible cases of undiagnosed CRPS and POTS. Brinth said that it would have been relevant to have these search strategies clearly defined and given because, to the best of her knowledge, there are no common search strategies which have been previously defined for either POTS or CRPS (5, pp35-36).

We wrote to the EMA that we agreed with Brinth. It is notoriously difficult to identify the harms in question and it is unacceptably poor standards for such research not to define precisely what the search strategies were. It is a fundamental requirement for systematic searches that the combination of search terms is clearly described so that the searches can be reproduced by others (26). In the EMA's internal 256-page report, however, we found some search strategies the companies had used when searching in their databases (4, pp29-31). We find these search strategies vastly insufficient. As just one example, the Uppsala Monitoring Centre has reported that for the largest clusters they identified in the WHO VigiBase(R), the most commonly reported AE terms were headache and dizziness and fatigue or syncope (23). They also found that the combination of headache and dizziness with either fatigue or syncope was found to be more commonly reported in HPV vaccine reports compared with non-HPV vaccine reports for females aged 9--25 years. The MAHs did not search for headache and they did not combine the terms in the way the Uppsala centre did. “Dizziness” needed to occur together with either “orthostatic intolerance” or “orthostatic heart rate response increased” in order to count, and there were other restrictions that must have led to many cases being overlooked. The EMA nonetheless uncritically reproduced the incidence rates of CRPS and POTS constructed by the manufacturers (15).

In its reply, the EMA “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 EMA's reply is worrying. The EMA agrees with us that cases are hard to find in searches and speaks about a conservative algorithm, which is supposed to find many cases. But they don't tell us what this algorithm is. As just stated, we found these algorithms (4), which were bound to miss many relevant cases. Further, as already noted, it can hardly be called a "conservative approach" when the method ended up discarding most of Brinth's carefully documented cases. Finally, the meaning of the EMA's many semantic subtleties continues to escape us. We do not understand what the EMA tries to tell us with its explanation of the word "common."

The EMA wrote to us: "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" (p9).

Essential issues in science should not be "available upon request." As just noted, we found two vastly insufficient algorithms used by the MAHs in the EMA's internal report and they also appear in an assessment report (25, pp24-26). A colleague provided us with a copy of "Rapporteurs' Day 150 Joint Response Assessment Report" from November 2014, which was an assessment of Gardasil 9 from Sanofi Pasteur MSD on behalf of the EMA (27). Although not being part of the EMA procedures we complain about here, it is nonetheless highly relevant for our complaint. The rapporteurs were concerned that Sanofi had avoided identifying possible cases of serious harms of the vaccine and their concerns were supported by the GCP [Good Clinical Practice] Inspection report (27, p79 and p101):

"The reporting procedure for AEs [adverse events] in this trial was complicated by the fact that as per protocol there was only specific, short, AE reporting periods in connection to each vaccination. In between, any new symptoms were only to be reported as 'new medical events' ... The information available about new medical events was however limited, as only symptoms were collected and no further medical assessments were made and no outcome was recorded. The reporting of SAEs [serious adverse events] was also not required during the full course of the trial ... in the inspectors' opinion it is not an optimal method of collecting safety data, especially not systemic side effects that could appear long after the vaccinations were given ... A potential concern is that there are 3 subjects in the clinical safety database who have been diagnosed with POTS, an on-going safety concern for the quadrivalent Gardasil, after receipt of Gardasil 9 and that in none of the 3 cases was the event of POTS reported as an AE ... Furthermore, for case AN29076, the Applicant should describe the rationale for inclusion of POTS as 'new medical history' instead of an AE given the report that it occurred 24 days post dose 1. For case AN71508, the Applicant should explain why the

hospitalisation for severe dizziness which occurred prior to the end of study visit was not reported as an SAE ... The Applicant should discuss, in the specific terms of case 37083, why the term 'dysautonomia' was not included on the line listing."

Again, this shows that the EMA's confidence in the work of the MAHs is totally misguided. The following example also involved Sanofi Pasteur MSD. When the DHMA in 2014 asked Sanofi Pasteur MSD to review its database for potential side effects of its HPV vaccine, the company searched for POTS in a way that made the number of cases retrieved very low (28). This was discovered by the Danish National Board of Health, partly because only 3 of 26 Danish reports of POTS showed up in the company's searches. Sanofi Pasteur MSD had been asked to search on a number of specific symptoms including dizziness, palpitations, rapid heart rate, tremor, fatigue and fainting, but the company ignored these clear orders. Instead, Sanofi Pasteur MSD searched on three symptoms: "postural dizziness", "orthostatic intolerance" and "palpitations and dizziness." As terms used in reports of harms are the ones used by the doctors reporting them, unusual search terms will yield few results. Just like the two algorithms did.

Interestingly, Brinth noted in her "responsum": "We use the exact same criteria" (those by Sheldon and Raj) (5, pp34-35), but many of her cases were nonetheless dismissed by the drug companies and subsequently by the EMA.

C9. Brinth noted that the EMA's question 2 to the companies did not make any sense to her because both the vaccine group and the control group received aluminium adjuvanted "placebo" or another aluminium adjuvanted vaccine as "placebo." She wondered why the EMA instructed the companies to only discuss potential explanations if a *difference* was observed. Brinth interpreted this as meaning that the EMA took it for granted that we knew with a very high degree of certainty that side effects due to the adjuvant would not be found (5, p37).

We told the EMA that we agreed with Brinth. In all the vaccine trials apart from a small one, the so-called placebo was not a placebo as it contained aluminium adjuvant, which is neurotoxic in high doses. It is therefore difficult to find a difference between harms of the vaccine and the "placebo," but the EMA failed to address this fundamental problem in its official report (2). It is clear from the EMA's internal report (4) that the MAHs simply lumped the results from trials with a genuine placebo with those that had a potentially neurotoxic "placebo": "**Clinical safety data.** For the purpose of the referral, the MAH was requested to provide an in depth review of the CRPS and POTS cases observed within all clinical studies. To respond to this request, the MAH has pooled the safety data from 18 completed and unblinded studies designed with an active comparator group (either placebo or another vaccine other than an HPV vaccine, i.e. Hepatitis B, Hepatitis A) which includes a total of 42,047 vaccinees (21,268 in HPV group and 20,779 in comparator groups)" (4, p119 in the pdf, or 7/67 in the subdocument). We believe this constitutes scientific misconduct, but the EMA accepted it, without reservations: "Strength of the potential association. The few cases reported from RCTs [randomised clinical trials] are evenly distributed between the qHPV and placebo groups which does not suggest an association" (4, p20 in the pdf, or p11 in the subdocument).

The EMA noted in its response to us: "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 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" (pp9-10).

We wonder if the EMA knows what a placebo is. The EMA called all studies placebo controlled, even those that use an active vaccine as "placebo," and accepted the analyses from the MAHs where they had lumped results obtained with a genuine placebo with those with something that was NOT a placebo. These active "placebos" could have similar side effects as the HPV vaccines, which would make it difficult or impossible to use the trials to find out if the HPV vaccines cause the suspected rare harms. We accused the EMA of scientific misconduct, but the EMA didn't respond to the serious issues we raised. The information the EMA provided is irrelevant for our complaint. Seven hundred people in a trial with a genuine placebo are clearly far too little to detect rare harms from a vaccine or a difference between trials that use saline injections and active comparators.

The EMA wrote to us: "For both vaccines development, the use of Al(OHh (5001Jg) 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 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" (p10).

We do not agree. The data are NOT valid for an evaluation of the possible harms of the vaccine when the control group is being treated with a potentially neurotoxic aluminium-containing solution. And we are not reassured by the EMA's statement that, "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". Drug regulators have all too often been wrong when they assured the public that there was nothing to worry about (11,16). Finally, the EMA did not explain what it meant by "maintain the double blinding of the studies and consequently the validity of data." This statement could be interpreted as implying that aluminium salts are so reactogenic that an inert placebo would cause far fewer reactions (systemic or local) and lead to quick identification of active substance recipients. If this is what the EMA means, it then also means that trials with "an active placebo" cannot be used to evaluate possible harms of the vaccines. Further, the outcome of primary interest in the trials is cervical cell changes, the assessment of which in routine practice is unlikely to be influenced by lack of blinding. The priority to maintain blinding while losing the possibility to investigate harms of the vaccines therefore raises concerns about EMA procedures.

The EMA wrote to us: "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.”

The clinical trials have been conducted and analysed by the drug companies, which have a huge interest in NOT finding any serious problems with their vaccines. In addition, we know that these conditions are vastly underdiagnosed and that it is therefore intensely misleading to compare the incidence in trials with the “estimated incidence of POTS and CRPS in the general unvaccinated population.” Finally, many more people are needed than those enrolled in the trials to detect if the vaccines cause very rare harms. The EMA disregards the fact that only 700 of these many patients were randomised to a genuine placebo.

The EMA did not ensure that all relevant trials were included in the assessments (15). The criteria for including trials are unclear (4), which one of the assessors commented on (4, pp 28-29 or 19-20 in pdf). The wording suggests that only data from useful trials were included, i.e. only those used to apply for licensing (4, pp 28-29 or 19-20 in pdf). For the qHPV vaccine, for example, the follow-up combined denominator (the total number of females) from trials presented by Merck Sharp & Dohme was 44,793 (15). Cross referencing the HPV vaccine trial numbers with the EMA trial holdings revealed that the EMA does not hold clinical study reports for these trials: V501-007, V501-011, V501-018, V501-020, V501-024, and V501-025 (15). The total number of females in these trials is 11,542. This means that the EMA cannot have possibly checked one-fourth of the manufacturers’ dataset ($11,542/44.793 = 25.7\%$). Conversely, at least four trials listed in the EMA’s qHPV holdings (or that are known to the EMA) are not included in the manufacturer’s list (15).

C10. Brinth criticised the EMA for asking the MAHs to provide an analysis of the observed number of post-marketing cases of CRPS and POTS in association with their HPV vaccine in comparison to those expected in the target population. Brinth argued that the analysis should discuss the assumptions made with respect to the background incidence in the target population and also the influence of potential under-reporting of cases in association with HPV vaccines. Brinth also noted that it is not possible for the time being to give a reasonable estimate of the background incidence “of these very underrecognized, underdiagnosed and poorly understood disease entities with very different diagnostic practices applied depending on nationality, medical specialty etc” (5, p39).

We agreed with Brinth and wrote to the EMA that one of the key arguments in the EMA’s report (2) was that there was no difference between what was observed and the expected background incidence. We explained that this observation was meaningless, as the underlying research was of very poor quality: “For example, for some of the analyses, the observed incidence of chronic fatigue syndrome was used to estimate the expected incidence of POTS (4, p96, or 87 in subdocument). Furthermore, the EMA writes in its report that for POTS with the Gardasil/Silgard vaccine, the observed number of cases was generally *lower* than expected under almost all assumptions for all regions and countries except for Denmark (2, p17). This observation should have alerted the EMA to the fact that analyses based on expected incidence are grossly unreliable. We find it curious and scientifically unacceptable that the official EMA report (2) puts more weight on the ‘observed versus expected’ analyses produced by the companies than the much more reliable Uppsala data.”

The EMA’s reply to us on this key issue was highly disappointing. The agency “acknowledged that the calculation of the background incidence rate in the relevant age population is difficult” and that “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.” Both the Belgian and the Swedish co-rapporteurs were highly critical of the observed versus expected analyses: “For both CRPS and POTS, the Co-Rapporteur considers that Observed vs expected methodology used in this CRPS analysis is based on many assumptions, which cannot be verified” (4, p210 or 31/77) and “The recalculation is therefore not considered helpful to reach the overall conclusion. The proposed recalculation of observed versus expected ratios is therefore not endorsed by CoRapp SE” (25, p9). Even the rapporteur was critical of these analyses: “Evidence from OE analyses cannot confirm a causal association due to the inherent limitations in spontaneous data” (4, p215 or 36/77).

However, the EMA’s official report does not reflect this substantial doubt about the trustworthiness of observed versus expected analyses (2). Quite the contrary. In no less than ten places in the 40-page report are these analyses used to convince the readers of the report that they should not worry about possible serious harms of the HPV vaccines:

“Observed versus expected (O/E) analyses cannot determine causality, but they are useful in signal validation and, in the absence of robust epidemiological data, in preliminary signal evaluation” (p13).

“The O/E analyses are generally reassuring” (p14).

“The analysis of O/E cases suggests that the number of observed POTS cases is low compared to those expected. The analyses are generally reassuring” (p15).

“The results of the O/E analysis for Gardasil/Silgard showed that the observed counts were less than expected in most scenarios of under-reporting, case definitions and risk periods” (p16).

“The results of the O/E analyses for POTS with Gardasil/Silgard showed that the observed number of cases was generally lower than expected under almost all assumptions for all regions and countries except for Denmark” (p17).

“The O/E analysis showed that the number of spontaneous reports of chronic fatigue following Cervarix vaccination was consistent with estimated background rates even assuming low reporting” (p31).

“Taking into account the O/E analyses, which do not suggest an increased occurrence of CRPS or POTS in relation to the HPV vaccines ...” (p37).

“Overall, the comparisons of observed versus expected number of spontaneous reports do not suggest an increased occurrence of CRPS in relation to the HPV vaccines” (p38).

“Overall, comparisons of observed versus expected number of spontaneous reports, with the same scenarios as described above for CRPS, do not suggest an increased occurrence of POTS in relation to the HPV vaccines” (p38).

“The PRAC considered that the observed versus expected analyses took into account a wide range of scenarios regarding underreporting and included reports that did not fully meet the diagnostic criteria for the syndromes. Overall, in these analyses the rates of these syndromes in vaccinated girls were consistent with expected rates in these age groups” (p39).

When “evidence from OE analyses cannot confirm a causal association due to the inherent limitations in spontaneous data” then, logically, they cannot provide any reassurance either for the opposite hypothesis, which is that the HPV vaccines are not harmful. We also wonder why the EMA put far more weight on analyses they admit are doubtful in its internal reports but not in its official report, than on much more reliable data produced by an independent researcher. The EMA put so much spin on something that doesn’t allow any conclusion to be made that we feel it could have been written by a PR agency working for a drug company. We therefore would like to know who

wrote or drafted the EMA's 40-page official report. No authors are listed on the report, which is another example of the lack of transparency and accountability and a possible attempt at sheltering behind the concept of corporate responsibility.

This does not foster public confidence in the EMA's impartiality.

The EMA wrote that, "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" (pp10-11). Brinth had argued that the analysis should discuss the assumptions made with respect to the background incidence, and we had agreed, but the EMA did not give us these assumptions but merely noted that they took account of possible under-reporting up to 99%. As we cannot check the analyses and the assumptions they are based on because we don't have access to them, we cannot comment on the EMA's postulates. Further, it is easy to say that the PRAC took the UMC data into account but we don't know how this was done.

C11. Brinth wrote that the EMA had asked the MAHs to provide a critical appraisal of the strength of evidence for a causal association between the HPV vaccine and CRPS and POTS considering the published literature (including epidemiological studies) and the possible causes and pathophysiology of CRPS and POTS, and to discuss whether there is a biological basis for a possible causal association. She wanted to know if this appraisal was performed by the MAHs only or supplemented by the EMA and highlighted that it would be highly relevant to know the search strategies applied in the literature research. She also mentioned that the current perception in the scientific field is that POTS is probably associated with autoimmunity, and that publications were starting to emerge that confirmed this view, and that autoantibodies are also found in CRPS and ME/CFS [myalgic encephalomyelitis/chronic fatigue syndrome] (5, p39).

We told the EMA that we found it totally unacceptable to perform a literature review without giving the readers details of its methods, in particular the search strategies used. This is the corner stone for such research, which is clear from manuals about systematic literature reviews, e.g. the Cochrane Handbook (26). We also found that the EMA had dismissed the research performed at the Danish Syncope Unit in a way that was unfair, misleading, partly erroneous and pejorative. We believe that if drug regulators behave like this when doctors report their observations about possible serious harms of approved products, doctors will be unlikely to alert the public to their observations in future. We consider that this would be a tragedy for public health.

The EMA's reply to us on this crucial point was very disappointing: "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." We had just pointed out to the EMA that it is totally unacceptable to perform a literature review without giving the readers details of the methods, in particular the search strategies used. Despite this, the EMA did not disclose any search strategy. This makes us suspect that the searches were scientifically inadequate, since, as the dictum goes: "If you have nothing to hide, then hide nothing." We have been unable to find the EMA's search strategies in any of the reports in our possession. The closest we came was this (29, pp62-64):

p62

- **HPV referral – literature search POTS**

The EMA has performed a systematic bibliographic search regarding Postural Orthostatic Tachycardia Syndrome:



p63

- **HPV referral – literature search CRPS**

The EMA has performed a systematic bibliographic search regarding Complex Regional Pain Syndrome:



p64

- **EVDAS search**

The EMA has performed a search in the EudraVigilance data base for cases of CRPS and POTS following vaccination with Cervarix. The obtained results are summarised below.

This speaks for itself. The EMA’s approach to literature searches is not only unscientific but the agency seems to be secretive about simple principles of methods. We doubt the EMA can provide any justification for redacting its search methods but would like to know why they were redacted. Redactions such as these make the EMA’s work not replicable and ultimately unaccountable.

The MAHs’ literature searches were grossly inadequate. When searching for CRPS, “The keywords for the search included ‘complex regional pain syndrome’ or ‘pain syndrome’ and ‘quadrivalent HPV vaccine’ or ‘Gardasil’” (4, p58) and when searching for POTS, “Keywords included ‘POTS’ or ‘tachycardia’ or ‘postural orthostatic’ and quadrivalent and 9-valent Human Papillomavirus vaccine (qHPV and 9vHPV)” (4, p69).

The EMA disagreed with our interpretation that, "the EMA had ridiculed and dismissed the research performed at the Danish Syncope Unit in a way that was unfair, misleading, partly erroneous and pejorative" with this argument: "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" (p11). The EMA’s argument actually confirms that its description of Brinth’s research is “unfair, misleading, partly erroneous and pejorative” since, contrary to what the EMA just asserted once again, Brinth DID mention the innate shortcomings of the methodology she used in her research. This was to such an extent that an independent researcher has concluded that Brinth’s research is clearly above the usual standard for such research (30).

Many redactions by the EMA in its documents are not legitimate

Various people have obtained redacted documents from the EMA through Freedom of Information requests, which they have shared with us. As we have access to the unredacted version of the EMA's confidential 256-page internal document (4), we can see which bits the EMA redacted. In our complaint to the EMA, we gave six examples of redactions that we found unreasonable (our comments are in brackets), reproduced here in their entirety:

D1. Names of contact people at the EMA for the rapporteur and co-rapporteurs. (This does not make sense, particularly since the names for the rapporteur and co-rapporteurs were not redacted).

D2. Case numbers of patients for which harms were reported. (This is not necessary, as it is not possible to identify individual people from a case number, but it can make it difficult to assess a scientific report when such numbers are missing).

D3. Country names for individual cases. (This does not make sense unless the idea is to obscure for outsiders whether or not the EMA's assessments are trustworthy, particularly since the EMA considers the Danish cases to be dubious).

D4. Numbers of reported harms for individual countries, names of countries where there is an excess incidence of reported harms, and number of doses of the vaccine used in individual countries. (This is even more difficult to understand unless the idea is to obscure for outsiders whether or not the EMA's report is trustworthy and whether or not the EMA's criticism of the Danish Syncope Centre is warranted).

D5. While it is indicated that some harms reports come from the Danish Syncope Centre, it is redacted that the centre is located at Frederiksberg Hospital. (This does not make any sense, particularly not when the name of the hospital was not redacted elsewhere).

D6. The publication identifier for an article in press. (This is pretty meaningless unless the idea is to keep readers of the report in the dark. Scientists routinely refer to papers in press and it should not be hidden where such papers will appear).

D7. Even more curious than the above redactions is the following: In the minutes from the SAG meeting on HPV vaccines on 21 October 2015 (24), the EMA had redacted not only what seemed to be 6 of 7 names of EMA staff (only Enrica Alteri was visible) but also 2 of 6 names for "PRAC Rapporteurs /assessors." We have not seen any explanation anywhere why we were only allowed to see who 4 of the 6 rapporteurs /assessors were: Julie Williams, Qun-Ying Yue, Jean-Michel Dogne and Ulla Wandei-Liminga. Elsewhere, e.g. in the 256-page internal report, only two co-rapporteurs and one rapporteur are mentioned (4), and we therefore thought there were only these 3 people and not 6.

When we asked the EMA why it had redacted names of some PRAC rapporteurs /assessors, we were told: "However, the document has been redacted 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 was redacted in order to avoid that the disclosure of the document would

undermine the privacy and integrity of any individual. In particular, names of PRAC assessors and EMA support staff have been redacted according to the Agency'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 veterinary use'" (18). We appealed to the EMA on 10 June 2016 saying (31): "We cannot understand why the EMA redacted some names but not others. Such selective redaction of names inevitably raises suspicions, e.g. about whether the redacted persons have important conflicts of interest in relation to the HPV vaccine manufacturers" and we asked for a document where no names had been redacted. The EMA responded on 11 July (see below under item D8).

D8. We also showed an example of an absurd redaction, which came from the "PRAC co-rapporteur's referral updated assessment report" (25). It is clear to anyone familiar with this area that the word left out must be "Denmark." The example also illustrates that there was far more uncertainty and disagreement than the EMA's official report reveals. The Swedish co-rapporteur (SE means Sweden) was obviously not happy with the approach taken and also criticises the observed versus expected incidence comparison of possible harms of the vaccine rather heavily, just like we have done.

Assessor's comment:

Given the substantial uncertainties in the observed versus expected analysis caused by the poor understanding of pathophysiology and unreliable definitions of these conditions and the consequent uncertainty regarding baseline incidence, a wide range of assumptions were used in these calculations. As noted, under some of these assumptions the observed already exceeds the expected in [REDACTED]. The suggested recalculation might actually increase uncertainty around the estimate. A wide definition of observed cases should be accompanied by a similarly wide definition in the estimation of expected cases in order to be correct. The recalculation is therefore not considered helpful to reach the overall conclusion. The proposed recalculation of observed versus expected ratios is therefore not endorsed by CoRapp SE.

The EMA's reply to us was totally unconvincing and it also demonstrated that the EMA no longer respects the ombudsman's ruling in our previous EMA case from 2010 (10). The EMA argued that all redactions made in the documents are in accordance with the requirement of the regulations and in line with the EMA's Policy and Rules. The EMA "has redacted all health data that could lead to the identification of a natural person," which includes date of birth, reporting country, patient identification code, patient numbers, case report numbers, 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" (pp11-12).

The EMA redacted much more in its HPV documents than the ombudsman considered necessary in 2010 when he noted that the documents we requested did not identify patients by name but by their identification and test centre numbers and that the only personal data are those identifying the study authors and principal investigators (10). In 2011, the Nordic Cochrane Centre requested clinical study reports on antidepressant drugs from the EMA, and some of these contained patient narratives (brief summaries of deaths, serious adverse events, or other events of clinical importance) or listings of adverse events in individual patients with details including the patient identifier (32). The fact that the patient identifier was not redacted (in fact *nothing* was redacted) meant that it was possible to compare information in the text of the reports with that in tables and narratives. This led

to the interesting discovery that four deaths were misreported by the company, in all cases favouring the active drug (32). It was also demonstrated, for the first time, that antidepressants double the incidence of aggression compared to placebo in children and adolescents (32), which can help explain why antidepressants may drive healthy people into committing suicide or homicide (16,33).

The AbbVie case shows that the EMA currently redacts a lot of information it should not have redacted (see item B9). We believe there is a strong overriding public interest in not having essential information redacted that can be important for patient safety. For example, we found important inconsistencies *within* the clinical study reports with respect to the reporting of adverse effects (32,34,35). The EMA's current approach, which we believe is illegitimate, can make research such as that on antidepressant drugs impossible.

The EMA provided a very long explanation when it disagreed with our view that "it is not possible to identify individual people from a case number," referring to a number of regulations and rules (p12). As noted above, all such documents are open to interpretation and the EMA seems to interpret them in the most restrictive way possible. Even so, the EMA is highly inconsistent in its decisions (10,15,20-22,32), and the minute risk of identifying a real person person needs to be weighed against the risk that many patients are being harmed and die because vitally important research about drug harms is being withheld by the EMA by all its unnecessary redactions.

The EMA noted that it redacts personal data, e.g. names, "of some EMA staff involved in pre- and post-authorisation activities" to protect the privacy of individuals, "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" (p12). We cannot understand why the EMA deletes names of people who are not involved with the scientific work and we doubt there are legitimate reasons for it. People who work with public administration for the common good should not hide who they are in an open and transparent society. On 11 July, the EMA explained that, "In particular, the exception applicable is in accordance with Article 4.1. (b) of the Regulation, whereby the Agency shall refuse access to a document where disclosure would undermine the protection of privacy and the integrity of the individual, in particular in accordance with EU legislation regarding the protection of personal data" (36). We fail to understand why a person's name can be regarded as "personal data" that needs protection because "disclosure would undermine the protection of privacy and the integrity of the individual ." By personal data, we understand, for example, a person's previous diseases and admissions to hospital. We believe the EMA's interpretations of the rules are highly questionable.

The EMA wrote: "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 website" (p13). Again, we cannot see any rationale for this sharp distinction between public servants in different roles.

The EMA noted: "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" (p13).

It is not correct that country names were not redacted and we gave an example above where "Denmark" was redacted. We have also observed that, in many countries, e.g. Denmark, detailed sales statistics are freely available on the internet making it possible for everyone to see how much of a given product that has been sold, in which regions and to which age groups, etc. It therefore makes no sense that the EMA interprets Regulation 1049 so narrowly and considers such data "commercially confidential information." Regulation 1049 can be overruled if there is an overriding public interest that is more important than to protect drug companies, which there surely is in this case. Without access to sales data, it is not possible to perform meaningful research on the incidence of serious harms possibly caused by the vaccines because no independent verification of denominators (number of doses sold or number of people vaccinated) used for rate construction can be carried out.

The EMA argued that, "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" (p13).

We find this argumentation bizarre. With the same type of argument, one could postulate that members of the European Parliament should all be anonymous and should all be wearing disguise when they debate in Parliament in order not to deter them "from having open and comprehensive discussion." In a democracy, people are responsible for their actions and opinions and should be held accountable for them. If people or public institutions have something to hide and hide it, it doesn't foster public confidence in the procedures or give them legitimacy, and it may open the door to corruption.

Corruption is very common in healthcare, and it also occurs at drug agencies, which the many scandals at the US Food and Drug Administration show (11). Corruption has also occurred in Europe, e.g. in Italy (11). Duilio Poggiolini, general manager of the pharmaceutical department of the Italian Ministry of Health, was arrested in 1993 due to a series of charges related to forgery and bribery favouring the entry of useless drugs (37). The scandal involved the minister of health who arranged for drug companies to pay bribes in order to get their drugs approved and sold at "suitable" prices (38). The corruption network also involved academics who received shares of the bribes in return for

expert advice in favour of the drugs, some of which were dangerous and sold at exorbitant prices. In 2008, the vice president of the Italian Drug Agency, Pasqualino Rossi, one of Italy's most senior representatives at the EMA, was arrested (39). Six drug company lobbyists were also arrested, and the case concerned alleged falsification of clinical data in return for cash, revealed by wire tapping and covert cameras. The prosecutor said the corruption had resulted in concealment of life-threatening harms of the drugs. The drug agency issued a statement that none of its employees were under investigation, but when the Italian press named the senior officials arrested, the statement was removed and a new one was being prepared. The fact that corruption occurs at drug agencies is a very good reason for being open about everything, including who said what. Secrecy makes it much more difficult to detect corruption.

The EMA noted that, "Regarding the mentioned publication identifier for an article in press that has been redacted, this has been an error" (p13).

Uncertainties in the science that were left out of the official report

We wrote to the EMA that there was much genuine uncertainty about what the science tells us and whether further research is needed, and that there was also a lot of disagreement in the EMA's working group that is not apparent in the official report. We gave some examples from "PRAC co-rapporteur's referral updated assessment report" from 28 October 2015 (25).

E1. The updated assessment report noted: "We agree with the limitations in the current data, but we do find it important not to dismiss the issue at this point but to consider studies or other activities to gain additional information in the future. Also we find that active communication and involvement of all relevant stakeholders is key to address current and future public concerns and ensure the public confidence in the national vaccination programs" (25, p9).

This didn't happen. The EMA left no doubt in its official report that the vaccine is safe (2).

The EMA wrote to us: "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 ... The PRAC (Co)-Rapporteur has reconsidered their [sic] 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 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" (pp13-14).

Much of the information obtained from the EMA is confusing. We thought the updated assessment report reflected the views of both co-rapporteurs because the report said "we" in several places. The EMA now tells us that it was the view of one of them only but nonetheless wrote, "The PRAC (Co)-Rapporteur has reconsidered their [sic] position."

We consider the EMA's explanation unsatisfactory. When there is genuine uncertainty in science about rare, but serious harms possibly caused by a preventive medical intervention in children, it is

not appropriate to use consensus methods and then convey to the public the impression that “everybody agrees that there is nothing to worry about.” The EMA has repeatedly stated that the benefits of the vaccine outweigh its harms. But that is not what the public is concerned about. The issue is whether or not some people are being seriously harmed by the vaccine. Although the EMA cannot rule out this possibility, it seems to us that the agency has nonetheless tried to do exactly this in its communications to the public. There is enough evidence to substantiate a suspicion of serious harms, which is what motivated the DHMA to call for an investigation. The EMA’s unwarranted certainty has been met with disbelief and has resulted in a dramatic decline in vaccine uptake, the exact opposite of what the EMA wanted. In Fyn in Denmark, the uptake of the vaccine decreased from 74% to 31% in just one year (40).

E2, 3 and 5. As the EMA replied to items 2, 3 and 5 together, we have inserted these replies, and our comments on them, after all three items.

E2. The updated assessment report noted: “In the search for cases coded as POTS in the database the MAH make a further selection by case definition criteria that appears too limiting. Only cases that are medically confirmed have been included, which is reasonable for a diagnosis such as POTS that cannot be expected to be verified by a consumer. 83 reports are identified as medically confirmed but out of these almost half (40 cases) are then dismissed for not meeting the case definition for POTS. It appears that they have been dismissed mainly due to lack of information in the reports. This does not appear to be in accordance with good practice, since spontaneous reports cannot be expected to describe all details for a diagnosis given to a patient. As also pointed out in the rapporteurs AR [we assume this means assessment report] p.22, we agree that when a diagnosis is reported and verified by a HCP [we assume this means health care practitioner], this description should be accepted and used in the further work e.g. observed versus expected ratios” (25, p9).

We wrote to the EMA that the “co-rapporteurs are highly critical of the approach of the MAHs and find that ‘when a diagnosis is reported and verified by a HCP, this description should be accepted and used in the further work e.g. observed versus expected ratios.’” We also said that it is noteworthy that the co-rapporteurs agreed with Brinth (see item C7 above) and that “this support for her arguments did not make it to the EMA’s official report (2). We believe that an assessment provided by a clinical expert who sees the patient is likely to be far more reliable than that performed by a company employee with a conflict of interest looking at paperwork.”

E3. The updated assessment report noted: “The main conclusion in the Danish report is not, as described in the assessment, to change focus to CFS. Rather the review highlights the necessity to evaluate combinations of symptoms rather than only performing separate evaluations of individual diagnoses. It shows that although the number of POTS cases is very high in Denmark, compared to the rest of the world, the symptom pattern seen in the Danish dataset is similar to reports submitted from other countries. Even though it cannot be shown for certain at this point, it is likely based on these data, that patients with the same symptomatology would receive different diagnoses in different member states e.g. POTS in DK and CFS/ME in others. This consideration is important for the discussion of consistency regarding the POTS signal, where it is stated that the finding of the majority of POTS cases in Denmark does not support a causal relationship. We do not agree with this conclusion based on the data” (25, p9).

The EMA's explanation to us that only one of the two co-rapporteurs was critical is misleading. Why say "We do not agree with this conclusion based on the data," if it is only one of them who disagrees? The co-rapporteurs (in plural, as we believe it is both of them) are highly critical of the EMA's draft report and yet again, they agree with Brinth, but this strong support for her arguments did not make it to the EMA's official report (2). The EMA told us that it was only the Belgian co-rapporteur that was critical, but we explained above (item D7) that also the Swedish co-rapporteur was critical of the approach taken and criticised the observed versus expected incidence comparison of possible harms of the vaccine rather heavily.

E5. The updated assessment report noted: "We support DHMA comment that due to differential clinical practice across countries, similar suspected ADRs [adverse drug reactions] to HPV vaccine are receiving different diagnoses (or indeed no clear diagnosis), which in turn may be potentially 'diluting' a safety signal" (25, p11).

The co-rapporteurs' support for the concerns of the DHMA that asked the EMA in July 2015 to assess possible serious harms of the vaccine were not included in the EMA's official report (2).

There are additional examples in the EMA's confidential, internal report (4) of important disagreements and observations that are not revealed in the official report (2). In several of these cases, the rapporteur disagrees with the two co-rapporteurs, but it is only the rapporteur's opinion that is presented in the official report.

The EMA wrote to us in relation to items 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" (p14).

Again, we can see no legitimate reason for the EMA to hide which Member State it is. We find it highly likely that the Member State is Denmark, since it was Denmark that raised the issue about vaccine safety, and since the Danish drug agency was critical towards the way the EMA assessed this risk. Politically, it is very common that a critical Member State expresses satisfaction if it is in a clear minority in a consensus discussion, but this whole affair is not about politics, it is about science. There is considerable public interest in knowing whether the disagreeing Member State was Denmark.

The EMA also wrote to us: "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.'" (p14)

The EMA misrepresents seriously the facts. We have explained above that the Belgian and the Swedish co-rapporteur agreed with Brinth on many important issues related to HPV vaccine safety!

E4. The updated assessment report noted: “However, as the potential involvement of Cervarix in the occurrence of CRPS cannot be completely ruled out at this stage, the co-rapporteur recommends that this risk should continue to be investigated” (25, p7).

“We agree with the conclusion from the rapporteurs and also state in the Danish report, that the data from spontaneous reports cannot be used to provide evidence for a causal relationship between symptoms and vaccination. However in view of the methodological limitations of the data available and the fact that the observed cases did exceed the expected cases, especially in Japan and Denmark, the conclusions should be cautious and the signal cannot be dismissed either based on the current evidence. We recommend that the vaccine SAG and expert meeting include a discussion of the need and possibilities to design appropriate PASS studies to explore POTS further. Similar question as Q3 regarding CRPS” (25, p10).

It was not specified in the assessment report who “we” are but “we” are highly likely the Danish Health and Medicines Authorities (DHMA). Again, it is not clear whether one or both co-rapporteurs agree with Brinth and the Danish authorities that more research is needed. The Danish authorities “agree with the conclusion from the rapporteurs,” i.e. both of them (25, p10). But this support for Brinth’s arguments was not included in the EMA’s official report (2). In the EMA’s confidential, internal report, the rapporteur dismissed the proposals by the Belgian co-rapporteur: “The Rapporteur agrees with most conclusions of the Co-Rapporteur (BE) for Cervarix, with the exception of the recommendations in relation to further evaluation of CRPS and POTS” (4, p5).

The EMA wrote to us: “In the first and fourth paragraphs, the statements of the Belgian Co-Rapporteur are presented ... 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 ... 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” (pp 14-15).

These statements are confusing. The EMA speaks about “three (Co)-Rapporteurs” although there were only two. And we are told, for the first time, that the “individual (Co)-Rapporteurs' assessment reports represent the view of individual teams.” This may explain why the dissenting co-rapporteur says “we.” The two co-rapporteurs were likely the most important of all the people that participated in the EMA’s processes, as they are those “who take the lead in the scientific assessment and who have the task of thoroughly assessing the data and draft their recommendations which is [sic] then shared with all PRAC members” (p4 in the EMA’s letter to us).

E6. We found this in the EMA's internal document: "Rapporteur's comments on the Brinth et al case series: ... In summary, the case series reported by Brinth et al represents a highly selected sample of patients, apparently chosen to fit a pre-specified hypothesis of vaccine-induced injury" (4, pp225-6 in pdf, or 46-47/77 in the subdocument). We wrote to the EMA that this defamatory remark about Brinth's research is exactly the same as in the EMA's official report: "apparently chosen to fit a pre-specified hypothesis of vaccine-induced injury" (2, p24).

The EMA replied: "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" (p15).

We believe that it is totally unacceptable that the EMA published (2) a remark that lacks any foundation and furthermore failed to mention that Brinth and her colleagues had themselves pointed out the well-known limitations of their research design. We also reject the EMA's argument that this should have anything to do with a critical assessment of the data and type of study from a "purely scientific perspective." If the EMA didn't intend to undermine Brinth's credibility, then why did the agency publish a sentence that could undermine a person's scientific reputation (4)?

E7. We wrote to the EMA that Dr Luc Kiebooms and Dr Andre Devos motivated in their submitted statements why a safety study was needed (4, pp171-4 in the pdf, or 59-62/67 in the subdocument):

"The Vioxx scandal² and Diane-35-problems have shown how weak [safety] reporting is. In both cases there has been reporting for years, but this was done with the same methodology as suggested here. So the insight into the actual extent and severity of the phenomenon was slowed down tremendously. In both cases afterwards it turned out, that the makers of the medicine knew of the adverse reactions, before the medication was brought into circulation. For HPV now, the same seems to occur. We are at the stage of a reporting of a particularly large number of cases for a vaccination, for which a zero tolerance regarding the side effects should prevail³. Until now all the literature is exclusively under the direct supervision of the industry, probably even all information comes from the industry. There are no independent studies, despite the fact that these were raised on several levels."

"Initially, the vaccine was compared with a placebo group being vaccinated with physiological serum, whereby the number of adverse reactions was much higher and much more serious than in the control group. After comparing 320 patients in the saline placebo group a quick move was made to an aluminium-containing placebo, in order to be able to only evaluate the effects of the active substance. However, this distorted the comparison, because no one voluntarily wants to be vaccinated with toxic aluminium, as this is not really necessary, when inoculation with a harmless saline solution can be done. The differences between Gardasil and the saline placebo group were, however, already noticeable¹⁵ the difference between the vaccine and the saline placebo is concealed in all publications, as the table below clearly shows. For serious adverse reactions one suddenly takes the saline and aluminium group together, perhaps to cover up the major differences between these two groups."

We wrote to the EMA that these two doctors questioned seriously the prevailing assumption, apparently also at the EMA, that the vaccine is so important for public health that it is justified not to communicate to the public that:

- 1) There are uncertainties related to vaccine safety;
- 2) Drug companies cannot be trusted; and
- 3) It is wrong to lump together results obtained with a genuine placebo with those obtained with a potentially neurotoxic placebo.

We agreed with the two doctors when they suggested that this lumping may represent a cover up and we also found that the EMA should have informed the public about this unacceptable lumping of a true placebo with an active placebo instead of keeping it secret. We noted that we found this totally unacceptable and contrary to good scientific practice to such a degree that we considered it outright scientific misconduct committed by the EMA.

The EMA replied to us that this was “the view of members of public who submitted spontaneous information which were included in the Belgian Co-Rapporteur's assessment report.” The EMA furthermore explained: “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” (p15).

It is not correct that the EMA ensures “maximum transparency, so that the European public can see how decisions were made.” It is clear from our complaint to the ombudsman that it is hard detective work to find out what went on in the HPV case and why, and we have spent months on this. As we have explained in detail above, not even the EMA's 254-page internal report comes any way near “maximum transparency.” We found out who the members of the PRAC and SAG committees were via other sources. This is more akin to police work than scientific work. The ombudsman needs to ensure that secret meetings at the EMA under a gagging clause will not be possible in future.

The MAHs presented their position during the open session at the SAG meeting. We believe that this should not be allowed. The companies can send what they have; they should not present at meetings because of their huge conflicts of interest and the psychology that is at play: Nice people tend to win arguments, and people may not ask critical questions in order not to “offend” the invited presenter.

We did not know who Dr Luc Kiebooms and Dr Andre Devos were but were told by the EMA (for the first time, which is not “maximum transparency”) that they were “members of public who submitted spontaneous information which were included in the Belgian Co-Rapporteur's assessment report.” This is very important information. The contributions of Kiebooms and Devos are the only ones in the whole 254-page report that alert people to the well-documented fact that drug companies cannot and should not be asked to audit their own work (11,16). Nonetheless, the EMA trusted almost blindly the two drug companies in the HPV case, which we believe is not a legitimate approach. The fact that the Belgian co-rapporteur included this information, which is highly critical of the drug

companies, in his report makes it even more unacceptable that this rapporteur was overruled in the “consensus” process, and that not a trace of his criticism was left in the EMA’s official report.

We believe that the EMA gets its task wrong when it argues that, “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.”

Firstly, the semantics are wrong. A benefit is a given, not something hypothetical, whereas a risk is hypothetical, as it may or may not happen. This is to turn things on their head. A drug, including a vaccine, ALWAYS causes harms, whereas we cannot know whether it has any benefits. Therefore, we should rather be speaking about the balance between potential benefits and certain harms, but we could also simply refer to the balance between benefits and harms (41).

Secondly, the balance between benefits and harms is highly subjective, and different people will reach different conclusions based on the same data. For example, although it is officially recommended to take influenza vaccination, many specialists in infectious diseases have declared publicly that they won’t take them. We do not believe that it is the primary task of a drug agency to come up with subjective statements or to recommend interventions. The EMA’s primary task is to ensure that the public gets as accurate and independent information as possible about the benefits and harms of the products it approves, so that they may decide for themselves whether or not they want to use the products. The EMA has not done this for the HPV vaccines.

Conflicts of interest

According to laws of public administration in several European countries, people should never be in a position where they are being asked to evaluate themselves or where they have a personal or financial interest in the outcome. For example, Danish law states (our translation):

“Anyone who works in the public administration is disqualified in relation to a particular case if he or she has a special personal or financial interest in the outcome ... The person who is disqualified in relation to a case does not make decisions, participate in decision making or otherwise assist in the consideration of the case.”

F1. The EMA stated in its internal report that the EMA asked the MAHs to provide “a cumulative review of available data from clinical trials, post-marketing and literature in order to evaluate the cases of CRPS and POTS with their product ... an analysis of the observed number of post-marketing cases of CRPS and POTS in association with their HPV vaccine in comparison to those expected in the target population, stratified by region, if available ... a critical appraisal of the strength of evidence for a causal association with HPV vaccine for CRPS and POTS ... The responses submitted by the different companies were assessed by the PRAC's Rapporteur (attachment 1) and Co-Rapporteurs (attachments 2 and 3) for this procedure. Before adopting a recommendation, the PRAC decided to convene the Scientific advisory group (SAG) on Vaccines and additional experts on vaccine safety, neurology and cardiology to provide an independent advice and responses to the questions below” (4, p5).

We noted in our complaint to the EMA that it is clear from its confidential document (4) that the EMA relied heavily on the companies to come up with honest answers to highly complicated

questions, and that the work of the EMA's various assigned experts was not to verify what the companies had done, but merely to summarise and discuss it. We found that this procedure provides poor protection of public health, particularly considering that there are so many egregious examples that companies have cheated by omitting major harms - including deaths - in their reports to the authorities (11,16). We found it unacceptable that the EMA did not check the veracity of the MAHs' work.

The EMA replied that, "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" (p15).

The EMA's reply is seriously misleading. Nowhere in the 254-page report is there any information that indicates that the data and analyses delivered by the drug companies had been "thoroughly and critically reviewed," the raw data re-analysed or even just checked. For example, as we stated under item C8, the EMA uncritically reproduced the incidence rates of CRPS and POTS constructed by the manufacturers. Furthermore, nowhere in the report is there any mentioning that any expert asked the companies for clarification of vitally important issues. If this had been the case, we would have expected to see a note about it, e.g. saying that one or more companies did additional analyses and describing what these analyses showed. We find it unacceptable that the EMA simply believed what the companies told them. The police don't believe what suspects tell them; they check it. And since it has been documented that the business model of drug companies involves deception (11), information that comes from them should always be "thoroughly and critically reviewed" and checked, just as the police would when dealing with known suspects.

The EMA also stated that, "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" (p15).

As we have explained above, a theoretical mechanism is not worth much if it is not being used when it is relevant to use it. It has been amply documented that companies often omit important data or seriously misrepresent them - also when they involve suicides and other deaths - in their submissions to regulatory authorities and that the authorities let them get away with it even when they are aware that they have been cheated by the same companies earlier in relation to the very same issues (11,16). Even when drug agencies find out that drug companies have been less than candid with lethal consequences, they don't require the companies to tell the public about the many deaths they omitted from their published clinical trial reports (11,16). In any case, we have provided mathematical proof that the EMA did not check what they already had available and did not ask for data that were not in their holdings.

The Nordic Cochrane Centre has worked with protocols and clinical study reports for antidepressant drugs submitted to the EMA for obtaining marketing authorisation, and by comparing the Index with what was obtained from the EMA, it became clear that whole subdocuments and appendices were missing (34,35). Other Cochrane researchers found that 15 of 16 study reports on oseltamivir for influenza received from the EMA lacked the appendices containing listings of effectiveness and adverse events, and there were no case report forms for important adverse events for any of the

trials (42). This suggests that the EMA does not check that they have received all relevant documentation when the agency decides to approve a new drug. This practice is also unacceptable. We are aware that, under Directive 2001/83/EC and ICH E3, appendices do not necessarily have to be submitted to the EMA as part of the regulatory submission for marketing authorisation, but the sponsor must make these available to the EMA on request (35). The “Note for guidance on the inclusion of appendices to clinical study reports in marketing authorisation applications” lists the appendices required to be submitted to the EMA with each clinical study report. These appendices include the protocol and amendments to the protocol. When the EMA doesn’t possess all documents, relevant independent research may not be possible, and the public might get misinformed by our drug regulators. In our experience, drug agencies are unwilling to contact the MAHs and ask for the missing documents. When the Nordic Cochrane Centre, for example, wanted to look at suicidality events in the extension phase of trials of the antidepressant drug, duloxetine, for urinary incontinence, the researchers found out that the EMA did not possess these important documents (43). The US drug agency (FDA) seemed to have them, as the agency stated that a higher than expected rate of suicide attempts was observed in the open label extensions of the controlled trials (43). Similarly, the EMA does not hold the Case Report Forms for serious adverse events reported in the HPV vaccines trials.

F2. At a hearing about HPV vaccine safety in the Danish Parliament on 17 December 2015, which was video recorded (44), Enrica Alteri from the EMA told the audience that the EMA’s Scientific Advisory Group consisted of members who were independent. However, she also said that they had declared their conflicts of interest (her remarks on this point were not translated by the simultaneous translation). As we explain below, some of these experts were not independent. Alteri told the audience that the HPV vaccine can prevent most, if not all, deaths from cervical cancer. She walked out immediately after her presentation with no excuse and did not take questions or participate in the panel discussion. This was perceived by some in the audience, which included Danish politicians, relatives of girls with severe symptoms, the media and scientists, as being blatantly arrogant and counterproductive in terms of building trust in the vaccines and in the EMA.

We wrote to the EMA that we found it totally unprofessional and misleading to the extreme to suggest that the HPV vaccine can prevent all deaths from cervical cancer. Such a claim would not have been tolerated by the EMA if it had come from one of the manufacturers. The EMA states itself in its publicly available report that the different vaccines don’t protect against infection from all HPV strains, only from 70%, 80% and 90% of the strains, respectively, and that the vaccines are not 100% effective against the targeted strains (2). We also found it inappropriate to use experts with financial ties to the manufacturers, as it is always possible to find experts without such conflicts.

The EMA provided a lengthy response to us on this important issue (pp15-17):

“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 ... 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.”

We find that all these rules and exceptions are so complicated and vague that it is impossible to apply them consistently, not only from case to case but even within the same case. The interpretation of the rules will also depend on who the chair is, and since chairs are allowed to have financial conflicts of interest in relation to drug companies, one would expect such people to be pretty lenient towards others with such conflicts. The whole setup is confusing and decisions are bound to be arbitrary and person-dependent. We consider this garbled situation as undermining the EMA's legitimacy. No one can remember all the detailed instructions when making judgments.

Some of the EMA's statements are wrong, e.g. “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.” The EMA doesn't do this, and according to the information we have, and the EMA's own statements quoted above, some SAG members and experts DID have such conflicts (see below). Enrica Alteri from the EMA therefore misled the audience in the Danish Parliament when she said that the EMA's Scientific Advisory Group consisted of members who were independent.

We find it unacceptable that “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” and we find it naive and unrealistic that the involvement of expert witnesses with such conflicts” is limited to testifying and giving specialist advice on a specific issue by providing information and replying to any questions only.” We also find it unacceptable that, “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.” It seems to us that the EMA knows very little about group dynamics. Abundant psychological research has shown that such precautions just cannot work as intended. The impact of all this on the EMA's credibility would be reduced if all limitations for all participants, with reasons, were made publicly available.

According to Danish law, people who are disqualified in relation to a case does not make decisions, participate in decision making or otherwise assist in the consideration of the case. The EMA needs to adopt a similar approach. Conflicted people should not have anything to do with the work at the EMA and should not be allowed to sit in committees, and if advice from them is needed, it can be obtained in writing. Everyone can understand and remember this simple and transparent rule, which is sensible, in contrast to the hopeless and garbled rules the EMA currently uses.

The EMA wrote to us that, “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” and “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.”

We believe it is impossible to ensure that a policy so complicated and vague “was correctly applied” as no two persons would be able to apply such intricate rules in the same way throughout an EMA process. Furthermore, the EMA was the judge for stating that the policy was correctly applied, which represents a conflict of interest in itself. As noted above, we asked the EMA to provide us with the names of the experts the EMA had used (18) and we also received minutes from the SAG meeting on HPV vaccines on 21 October 2015 (24). Four people were not allowed to take part in the final conclusions of the meeting because of their declared conflicts of interest. As the minutes from the meeting did not specify what these interests were, we consulted the EMA’s website. Martin Ballegaard was investigator on a study by Novartis in infants with type 1 spinal muscular atrophy. Rolf Karlsten had multiple conflicts of interest in relation to drug companies and owned shares in a company. Jesper Mehlsen was involved with a trial of an HPV vaccine from Merck, Sharp & Dohme. Frank Huygen had been on the Advisory Board of Grünenthal till 2015 and of GlaxoSmithKline in relation to its HPV vaccine till 2013.

There were no restrictions for the chair of the meeting, Andrew Pollard, although he had declared several conflicts of interest in relation to the HPV vaccine manufacturers GlaxoSmithKline and Sanofi Pasteur MSD until 2014 and 2013, respectively. In an article dated 24 September 2015 (while the process at the EMA was ongoing and one month before the SAG meeting), which described a 12-year old girl that had been diagnosed with chronic fatigue syndrome after having been vaccinated, Pollard, the “chairman of the government’s Joint Committee on Vaccination and Immunisation (JCVI),” was quoted as saying (45): “We have no evidence of a safety signal with the vaccine. But what we do have is very clear evidence that this year 900 women, who have not received the vaccine, will die of cervical cancer, and the vaccine has the potential to prevent such deaths in future generations. So the place of this vaccine in defending women’s health is probably the most important thing we have ever done.”

We expressed our consternation over all this to the EMA on 10 June 2016 (31) and appealed its decision to redact the names of some of the co-rapporteurs and the names of most of the EMA’s own staff. We noted that Pollard, who was a member of the expert group of the British government responsible for the decision to include HPV vaccination in the childhood vaccination program in the UK, seemed to have participated in the meeting with a predetermined opinion on the issue of POTS/CRPS prior to the formal review of the data, and that, in a court of law, such evidence of partiality prior to a trial would be grounds for exclusion from the jury. We asked the EMA to inform us of its justification for offering the chair of the SAG, Andrew Pollard, privileges that were denied others with similar or fewer conflicts of interest than the chair.

The EMA replied on 11 July (36). The EMA had redacted the identity of the PRAC Assessors, “who are officials of the competent authorities of the EU Member States and are neither PRAC Members nor EMA experts nor EMA staff,” in accordance with Article 4(5) of the Regulation and an “Output Table” that was discussed and adopted by the EMA Management Board which includes representatives from the EU Member States. However, following our appeal to the EMA, the “EMA consulted exceptionally, taking into account this specific situation, the relevant EU Member States regarding the release of the identity of their assessors notwithstanding the provisions of the Output Table. As a

result, the Agency is now in a position to release the PRAC Assessors' names. Furthermore, the Agency will consider amending the provisions of the Output Table for future instances.”

The names of the three PRAC assessors were Rolf Gedeborg, Phil Bryan and Suzie Seabroke. According to the EMA’s website, they did not have conflicts of interest.

The EMA did not respond to our pertinent questions related to Pollard other than providing a nonsense reply, considering the substance of our observations:

“Finally, with regard to your claim of a potential conflict of interest of the SAG's chair, please note that the European Medicines Agency 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.” After this came some general statements about the EMA’s procedures and “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.”

This demonstrates that the EMA’s policy was NOT correctly applied. It is pointless to exclude a person from parts of the meeting who is investigator on a study by Novartis in infants with type 1 spinal muscular atrophy, which has nothing to do with the HPV vaccine, while allowing the chair of the meeting to attend the whole meeting although he had recent conflicts of interest in relation to the HPV vaccine manufacturers, and who in the press had praised highly the vaccines one month before the crucial SAG meeting. Pollard spoke about the many lives it saved and said there was no evidence of safety problems. The statement about the lack of harms was clearly inappropriate to make for a chairman of an EMA committee in the middle of an ongoing process to assess whether or not there is a safety signal. Furthermore, we found out that Enrica Alteri from the EMA, who had no restrictions on her participation, nonetheless had conflicts of interest declared on the EMA’s website. She was employed by Merck-Serono till June 2012 and her husband has a consulting contract with Merck-Serono for 2016.

There were other reasons why the EMA’s policy was not correctly applied. As we stated under item B7 above, we could not find any conflicts of interest declarations for two core members of the SAG on the EMA’s website when we checked it in May 2016.

We hope the ombudsman will ask the EMA to respect the rules in future and also ensure that neither chairmen nor other members of EMA committees have current or recent conflicts of interest.

The EMA wrote to us that the feedback provided to the agency from the meeting in the Danish Parliament was that Enrica Alteri’s presentation was very well-received, but did not specify who provided the feedback. If it was Enrica Alteri herself it would not count much, and it is difficult to know how it was received when no questions or comments were allowed. One of us spoke with several people after Alteri’s presentation, including one who had participated in one of the EMA’s HPV vaccine committees and they were all very negative towards Alteri’s presentation, which was perceived as arrogant and glossing over all the problems and disagreements that had been apparent at the committee meetings.

F3. In our complaint to the EMA, we wrote that we believed that the EMA’s rapporteur Julie Williams had conflicts of interest she had not declared on the EMA’s homepage. We apologize for this

mistake, which stems from the limited information that was available to us. In the material from the EMA that we had acquired, we could not see where this person worked and therefore looked the name up on the Internet. Unfortunately, we found the wrong person, another Professor Julie Williams. Therefore, what we wrote about Professor Julie Williams in our complaint to the EMA should be disregarded, apart from the sentence where we stated that she had declared no conflicts of interest on the EMA's homepage.

F4. We wrote in our complaint to the EMA that the EMA's executive director, Guido Rasi, declared on 20 July 2015 that he had no conflicts of interest (46). On a form called "EMA Public Declaration of Interests," he replied "none" to all four questions, also to question 4, which is: "Other interests or facts whether or not related to the pharmaceutical industry⁴ which you consider should be made known to the Agency and the public, including matter relating to members of your household⁵."

We also wrote: "However a Guido Rasi, which we assume is the same person, holds a number of patents, some of which were filed or approved in 2012 or 2013, and where the applicant was a drug company (Applicant: SciClone Pharmaceuticals, Inc.; Inventors: Guido Rasi, Enrico Garaci, Francesco Bistoni, Luigina Romani, Paolo Di Francesco) ... As they go back less than five years, we believe Rasi should have declared them, according to the EMA's regulations concerning the handling of declared interests of its employees" (47,48).

Finally, we wrote: "The EMA's director, Guido Rasi, has brought in a number of people from the drug company Sigma Tau that include Stefano Marino, his head of legal affairs. Rasi has worked with this company for many years and apparently owns several patents together with the company" (47).

This issue resulted in a long correspondence, which we believe has considerable public interest. The correspondence included letters from Guido Rasi's law firm marked "Private and confidential." As there is nothing private in them and we have not signed a confidentiality agreement with this law firm or with Guido Rasi, and as we believe there is an overriding public interest in making our correspondence publicly available that trumps any commercially confidential information we might have overlooked, we have decided to include the entire correspondence in the Appendix to this complaint to the ombudsman.

The first letter we received was written by the EMA's Deputy Executive Director, Noël Wathion, 17 June 2016 (see appendix). Wathion wrote:

"EMA would like to refute your unsubstantiated allegations in the strongest possible terms ... Amongst other things, EMA staff members are required to declare in their declaration of interests (DoI) any ownership of a patent held for a period of 5 years prior to the start of employment with the Agency ... An inventor ... is not necessarily the owner of the patent, e.g. the ownership rights may be vested originally upon, or subsequently assigned to, a subject other than the inventor/s. Only the owner of a patent can enjoy economic rights with regard to that particular invention. Therefore, neither the applicable rules, nor considerations of common sense oblige EMA staff to declare in their DoI any patents for which they are the inventor/s, but not the owner/s, unless the inventor is entitled to financial benefits (e.g. lump-sum or royalties) stemming from the exploitation of the invention ... An expert is required to declare such an interest if the patent is owned by the individual or if the individual is directly a beneficiary of the exploitation of the patent ... The Agency's Executive Director Prof Rasi is indeed mentioned on a number of patents, even beyond those referred to in

footnote 15 of your complaint letter, but only as inventor, not as owner of the patents. Prof Rasi does not own any patent together with Sigma-Tau. He is named as inventor on 2 patent families for which Sigma-Tau is named as applicant or patentee. He is not even the beneficiary of those patent families. Hence there was and there is no obligation for him to declare these patents in his DoI as EMA staff member in accordance with EMA's proceedings on the handling of DoIs ... We would also like to clarify that Prof Rasi has never worked with or for Sigma-Tau and that no former Sigma-Tau employee joined EMA since 2011 with the exception of Mr S. Marino, who was indeed the former General Counsel at Sigma-Tau, as publicly announced by EMA when he was hired after a very rigorous competition run by a selection panel featuring also external members from the Legal Service of the European Commission. Prof Rasi was not part of that selection panel and he did not know Mr Marino when he was still working in industry ... Taking into account the seriousness of the accusations made via the Internet and the echo that these allegations have had worldwide, EMA reserves the right to protect its reputation through all appropriate means."

Wathion wrote that, "A reply to the other issues you have raised in your complaint letter is being finalised and will be provided to you within the next few days." We therefore decided not to reply to Wathion's letter separately but to wait for the EMA's main reply to us. However, we did not receive the main reply before the holiday season had started for some of us.

On 8 July, Guido Rasi's lawyers, Carter-Ruck solicitors in London, which describe themselves as "One of the UK's best-known law firms, Carter-Ruck has a longstanding reputation for its expertise in the field of litigation and dispute resolution," sent us a letter. Their letter alleged that our comments about Rasi were "highly defamatory" and stating that a consequence of our letter should have been that, "Mr Marino, far from securing his role at EMA through proper and transparent means and solely on merit, is strongly to be suspected of having benefited from nepotism and improper patronage on the part of Professor Rasi." The lawyers wrote that "in Professor Rasi's case, he had never, and does not, have any economic rights or financial interest or benefit (whether actual or potential) in, or arising from, any of the patents to which the Publication refers. That being the case, Professor Rasi was and is not under any obligation to declare his status as a mere inventor of certain patents in his EMA declaration of interests; indeed it would make no sense for him to do so." The lawyers made it clear that their client did not wish to become embroiled in a legal dispute but that he hoped that we would agree "to amend the relevant passages of the Publication, and to publish (in terms to be agreed) a suitable statement of correction and apology withdrawing these false allegations."

Because of holidays, we could not respond before 12 August. We explained that, as researchers, we believed it would be wrong to change published documents. If errors are detected in scientific papers, the papers are not changed but errata are published separately. We had therefore written a separate document, which we attached and aimed to publish on the Nordic Cochrane Centre's website, alongside our complaint to the EMA from 26 May. In this document, we described the issues in detail, apologized for the mistakes, and explained: "We were not aware of the legal subtleties and assumed that an inventor of a patented technology is also an owner of that patent, as it is highly unusual that inventors give away their patents to drug companies without benefiting from them and without having any working relationship with that particular company. As concerns the employment of people, there are legal procedures to follow, but it is also very common that the employer contacts people informally, encouraging them to apply for the post."

On 18 August, the lawyers wrote that Rasi could not accept our wording and they sent a revised version, which they trusted was uncontroversial. We found that version unacceptable because we were asked to accept statements as facts, although we had had no possibility of checking these facts ourselves (see below).

On 25 August, we wrote that an apology is a very personal thing, and that, in our opinion, the person asking for an apology should not require a particular text or format, as the apology would then not be genuine. We tried to compromise but made it clear that we also needed to protect our own reputations and therefore needed to explain to the readers of the document that our mistakes were made in good faith. Therefore, we could not accept that our explanations had been deleted. We also noted that these explanations were helpful for the readers of the document and therefore had general public interest, and we added that both the EMA and ourselves serve the public interest. Finally, we asked the lawyers to take into account that four of us are scientists and the fifth is a politician. In these capacities, we can write what others have told us, making it clear that this is what they told us, but we cannot allow ourselves to be forced to accept such statements as fact when we have had no possibility of checking these facts ourselves.

We proposed that our apology should include our explanations adding:

“Noel Wathion has explained to us that Professor Rasi is not the owner of the patents for which he is named as inventor” and “The EMA has stated to us that Professor Rasi did not bring anyone to EMA from Sigma-Tau and that Stefano Marino was recruited according to the ordinary, rigorous EU selection procedures and received no favourable treatment at all.”

We were convinced that this would settle the issue. But on 24 August, the law firm wrote: “Our client considers that the wording of the errata document is most of the way there, albeit it is still not acceptable in its current form. Rather than engage in further protracted correspondence, we propose a telephone discussion to try to resolve any remaining issues. Please confirm if you are amenable to this approach, and if so please let us know when would be convenient.”

Given our experience with lawyers, we responded: “We prefer to communicate in writing.”

On 7 September, we received a letter from the lawyers saying again that the wording in our document “is most of the way there.” However, some important issues remained. We needed to reiterate that we cannot be forced to accept statements as fact when we have had no possibility of checking these facts ourselves. We furthermore said that lawyers know very well that, in court cases, one cannot force people to accept and declare what others tell them is the truth. We therefore could not accept the suggested amendments, which included this sentence: “On the basis of these assurances we accept that Professor Rasi has never had, and does not have, any economic rights or financial interest or benefit (whether actual or potential) in, or arising from, any of the patents to which the Publication refers.”

On 16 September, we received another letter from the lawyers requesting that we should insert this sentence: “We acknowledge Mr Wathion's statement that Professor Rasi has never had, and does not have, any economic rights or financial interest or benefit (whether actual or potential) in, or arising from, any of the patents to which the Publication refers.”

We responded that, “Firstly, your suggested amendment misses the context. Secondly, Wathion has never made any such statement to us; this statement was made by Rasi’s lawyers, Carter-Ruck solicitors. Thirdly, the amendment is not necessary, as we had already previously acknowledged Wathion’s explanations.”

On 30 September, we received the 8th letter from Rasi’s lawyers, which said that “Our client is prepared to accept your proposed wording of the apology, as it is imperative that the public is alerted as to the true state of matters, and in addition he has no desire to engage further in protracted correspondence and mutual inconvenience.”

This ended a protracted correspondence that started almost three months earlier. We uploaded our apology (see the Appendix), which noted that we had submitted a complaint to the EU ombudsman over maladministration at the EMA related to safety of the HPV vaccines the same day.

We did not at any point in time hear from Rasi himself, only from his deputy and his law firm. We find the EMA’s various arguments in relation to Rasi’s declaration of interests untenable. Whatever the rules are, a top executive in an EU institution should ensure that not the slightest suspicion can be raised that he failed to declare his conflicts of interest. A rule of thumb that is often quoted and used is that if a normal person would be embarrassed if real or possible conflicts of interest were revealed that had not been declared, then it was wrong not to declare them. Rasi failed this simple and sensible test. We therefore rejected the EMA’s and the law firm’s common sense explanations. The EMA argued that “neither the applicable rules, nor considerations of common sense oblige EMA staff to declare in their DoI any patents for which they are the inventor/s, but not the owner/s, unless the inventor is entitled to financial benefits.” And Rasi’s lawyers explained that, “Professor Rasi was and is not under any obligation to declare his status as a mere inventor of certain patents in his EMA declaration of interests; indeed it would make no sense for him to do so.”

It would have made a lot of sense for Rasi to declare this, also considering that Rasi is Italian and Sigma-Tau is an Italian drug company. It is extremely unusual for inventors to give away their patents to a drug company without benefiting from them in one way or another and without having any working relationship with that particular company. It is so unusual that we had never heard of any such case before we were told that this was the case for Rasi. Another reason why it would have made sense for Rasi to declare his patent inventions has to do with the legitimacy of the EMA in the public eye. The general public has so little confidence in the drug industry that it is similar to the confidence they have in tobacco companies and automobile repair shops (11). Furthermore, the general public has been informed in newspaper articles and TV documentaries that corruption at the upper levels of drug agencies occurs. The corruption has included several commissioners of the US Food and Drug Administration (11). FDA commissioner Lester Crawford approved Vioxx, a deadly arthritis drug from Merck that is estimated to have killed 120,000 people (11), and he left the agency after Merck had withdrawn Vioxx from the market. After resigning, Crawford became senior council for Merck’s PR firm, Policy Directions Inc. He later received a fine of \$90,000 for falsely reporting he had sold stock in companies regulated by the FDA while he still owned the shares. These companies included Pepsico, which sells soft drinks and junk food that make people obese, and at the same time, Crawford was head of FDA’s obesity working group. Such cases illustrate why top executives in drug agencies should declare even remotely, possible conflicts of interest, which might raise suspicion if not declared.

Final remarks

The EMA should have considered that when doctors first alerted the scientific community to the possibility that Pandemrix, one of the influenza vaccines used during the 2009-2010 pandemic, could be related to the occurrence of narcolepsy in children and adolescents with a specific tissue type, the reaction was to ridicule these doctors. It has now been firmly established that Pandemrix can cause narcolepsy, a very serious condition, *up to several years after vaccination of children and adolescents*, and that this disease is immune-mediated. However, there was nothing about this, neither in the EMA's official report (2), nor in its confidential report (4).

The bottom line for the EMA seems to have been that the vaccine should be protected from criticism at all costs because it is believed to save lives. One sign of this is that the text in the official report is nearly identical to the assessments of the rapporteur and the companies.

Sloppy science, combined with unprofessional and unfair criticism of independent research, such as the one the EMA raised against the diligent Danish researchers, is a serious threat to scientific progress and public health. Those who raise concerns should be complemented for their courage, even if their suspicions are later shown to be wrong. Indeed, it is a requirement by DMHA that Danish doctors raise concerns they might have. Unfounded criticism of whistleblowers from those at the top of overseeing agencies is potentially highly damaging, as it may prevent important concerns from being raised. Brinth reported in her "responsum" that she had been contacted by quite a few doctors and researchers from various countries who shared her concerns and had seen the same pattern, but that most of them were afraid to speak up (5, p51). She found that we have established a culture where it is not acceptable to have a critical approach towards vaccines. This could create much greater problems than declining uptake rates in HPV vaccination programmes. Should the concerns over possible serious harms of the HPV vaccine be confirmed, the trust in the EMA and in vaccines in general may be damaged beyond repair.

Since we submitted our complaint to the EMA on 26 May 2016, we have been made aware of several upcoming studies that provide data in support of the autoimmune causal theory (23; see also the discussion section in this paper). It is possible that most seriously ill girls suffer from an autoimmune disorder, and not from a functional disorder (i.e. a psychiatric disorder), as has been proposed. These upcoming data cannot prove that it was the HPV vaccines that caused the serious harms, but it should be a research priority to find out.

The secrecy imposed by the EMA on its committee members is not in the public interest. Drug regulators tend to have a narrow vision, either because of their remit or because they have become too close to the drug industry through their daily work, which often involves contacts with the industry, and by employment of people with long careers in the industry. We hope the ombudsman will ask the EMA to halt this practice.

Public health is about the promotion of health and prevention of disease and disability through the organised efforts of society. This entails protection from harms and involves progression of knowledge in open collaboration. As far as we can see, the actions of the EMA in this case indicates that the agency is more concerned about protecting its own previous decisions and the vaccines than about protecting the citizens and giving them the option of choosing for themselves whether or not they would like to get vaccinated or have their children vaccinated against HPV. Citizens don't

appreciate a paternalistic statement that all is fine based on inscrutable research conducted by the drug companies (2). Most girls and women will get vaccinated, but some will prefer to avoid the vaccine, even if the risk of serious harm is very small. Others will prefer screening instead.

We wrote in our complaint to the EMA that all available material about suspected harms of a public health intervention directed towards healthy children, including intermediate reports, should be accessible to anyone. The EMA's internal report (4) and all other documents related to this case should therefore be made publicly available, without redactions. We also noted that we did not find any commercially confidential information anywhere in the documents we reviewed. The EMA's procedures for evaluating the safety of medical interventions need to be fundamentally reworked and made transparent to the public.

Finally, our societies should no longer accept that assessments of drug safety are left to companies with huge financial interests and to a drug regulator that receives 80% of its funding from the drug industry (49) and allows experts with financial conflicts of interest in relation to the companies to guide them. In court cases, jurors are carefully selected to avoid bias. The same principle should apply to experts who make decisions that have consequences for our health and survival.

We will end by quoting Silvio Garattini, a former Italian representative at the EMA, who published a paper in BMJ in 2016 with the title: "The European Medicines Agency is still too close to industry: Two decades after its inception, the agency still fails to put patients' interests first" (49).

References

- 1 Peter C Gøtzsche, Karsten Juhl Jørgensen, Tom Jefferson, Margrete Auken, Louise Brinth. Complaint to the European Medicines Agency (EMA) over maladministration at the EMA. 26 May 2016. Available at <http://nordic.cochrane.org/research-highlights>.
- 2 European Medicines Agency. Assessment report. Human papilloma virus (HPV) vaccines. 11 November 2015 (40 pages).
- 3 Danish Health and Medicines Authorities. EMA's new assessment of the HPV vaccine: The benefits outweigh the risks. 17 April 2015. <https://sundhedsstyrelsen.dk/en/news/2015/emas-new-assessment-of-the-hpv-vaccine-the-benefits-outweigh-the-risks>.
- 4 Briefing note to experts. EMA/666938/2015. 13 October 2015 (256 pages).
- 5 Brinth L. Responsum to Assessment Report on HPV-vaccines released by EMA November 26th 2015. 17 December 2015. <http://www.ft.dk/samling/20151/almdel/suu/bilag/109/1581470.pdf>.
- 6 Regulation (EC) No 1049/2001 of the European Parliament and of the Council of 30 May 2001 regarding public access to European Parliament, Council and Commission documents. Official Journal of the European Communities 2001; L145: 43-8. www.europarl.europa.eu/RegData/PDF/r1049_en.pdf.
- 7 Letter from Noël Wathion to Peter C Gøtzsche, 17 June 2016 (available in Appendix).

- 8 Letter from Noël Wathion to Peter C Gøtzsche, 1 July 2016 (available in Appendix).
- 9 Letter from Carter-Ruck solicitors on behalf of their client, Guido Rasi, to Peter C Gøtzsche, 8 July 2016 (available in Appendix).
- 10 Gøtzsche PC, Jørgensen AW. Opening up data at the European Medicines Agency. *BMJ* 2011; 342: d2686.
- 11 Gøtzsche PC. *Deadly medicines and organised crime: How big pharma has corrupted health care*. London: Radcliffe Publishing, 2013.
- 12 Schroll JB, Penninga EI, Gøtzsche PC. Assessment of Adverse Events in Protocols, Clinical Study Reports, and Published Papers of Trials of Orlistat: A Document Analysis. *PLoS Med* 2016; 13: e1002101.
- 13 Diamandouros PN. Ombudsman: European Medicines Agency should disclose clinical reports on anti-obesity drugs. European ombudsman press release, 7 June 2010. www.ombudsman.europa.eu/press/release/faces/en/4940/html.bookmark.
- 14 Hawkes N. Lobby groups call for closure of ‘revolving door’ between drug regulators and industry. *BMJ* 2011; 343: d8335.
- 15 Jefferson T, Jørgensen L. Human Papilloma Virus (HPV) vaccines, Complex Regional Pain Syndrome (CRPS), Postural Orthostatic Tachycardia Syndrome (POTS), and autonomic dysfunction: a review of the regulatory evidence from the European Medicines Agency (EMA). *Indian J Med Ethics* 2016 (submitted).
- 16 Gøtzsche PC. *Deadly psychiatry and organised denial*. Copenhagen: People’s Press; 2015.
- 17 Trojaborg K. Danske forskere sables ned: Ingen sammenhæng mellem HPV vaccine og alvorlige symptomer. *Politiken* 2015 Nov 26.
- 18 EMA. Article 20 referral, HPV vaccines- ASK-20511- Release letter to the requester. 2016 June 9.
- 19 Watson R. European ombudsman questions European Medicines Agency over AbbVie redactions. *BMJ* 2014; 349: g6904.
- 20 Gøtzsche PC. AbbVie considers harms to be commercially confidential information: sign a petition. *BMJ* 2013; 347: f7569.
- 21 Tom Jefferson et al: EMA’s data sharing policy - towards peeping tom based medicine? *BMJ* 2014; 22 May. <http://blogs.bmj.com/bmj/2014/05/22/tom-jefferson-et-al-emas-data-sharing-policy-towards-peeping-tom-based-medicine/>
- 22 Tom Jefferson and Peter Doshi: EMA’s double U-turn on its Peeping Tom policy for data release. *BMJ* 2014; 13 June. <http://blogs.bmj.com/bmj/2014/06/13/tom-jefferson-and-peter-doshi-emas-double-u-turn-on-its-peeping-tom-policy-for-data-release/>

- 23 Chandler RE, Juhlin K, Fransson J, Caster O, Edwards R, Noren GN. Current safety concerns with human papillomavirus vaccine: a cluster analysis of reports in Vigibase (R). *Drug Saf* 2016 Sept 16.
- 24 Minutes and responses to PRAC from the SAG Vaccines meeting on HPV vaccines (Article 20 referral) (GlaxoSmithKline biologicals, Sanofi Pasteur, Merck). 21 October 2015, 9:30-15:30 - Room 2F - Chair: Prof Andrew Pollard. London, 4 Nov 2015. Doc. Ref.: EMA/702401/2015. Confidential.
- 25 PRAC co-rapporteur's referral updated assessment report. Updated report circulated 28 October 2015.
- 26 Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0. The Cochrane Collaboration, 2011.
- 27 Dunder K, Mueller-Berghaus J. Rapporteurs' Day 150 Joint Response Assessment Report. Gardasil 9. 2014 Nov 23.
- 28 Weber C, Andersen S. Firma bag HPV-vaccinen underdrev omfanget af alvorlige bivirkninger [The company behind the HPV vaccine underestimated the prevalence of serious side effects]. *Berlingske* 2015; 26 Oct.
- 29 PRAC (co)-rapporteur's referral 2nd updated preliminary assessment report. Updated report circulated 28 October 2015.
- 30 Palshof T. En analyse af EMA's kritik af 3 danske videnskabelige publikationer vedrørende rapporterede bivirkninger fra danske piger og kvinder opstået i tilslutning til HPV-vaccination. Et responsum til offentlig brug - version 3.0. 2015 Dec 10.
- 31 Nordic Cochrane Centre. Re: Ask-20511, about the safety of the HPV vaccines. 2016 June 10.
- 32 Sharma T, Guski LS, Freund N, Gøtzsche PC. Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses based on clinical study reports. *BMJ* 2016; 352: i65.
- 33 Bielefeldt A, Danborg P, Gøtzsche PC. Precursors to suicidality and violence on antidepressants: systematic review of trials in adult healthy volunteers. *J R Soc Med* 2016 (in press).
- 34 Maund E, Tendal B, Hróbjartsson A, Jørgensen KJ, Lundh A, Schroll J, Gøtzsche PC. Benefits and harms in clinical trials of duloxetine for treatment of major depressive disorder: comparison of clinical study reports, trial registries, and publications. *BMJ* 2014; 348: g3510.
- 35 Maund E, Tendal B, Hróbjartsson A, Lundh A, Gøtzsche PC. Coding of adverse events of suicidality in clinical study reports of duloxetine for the treatment of major depressive disorder: descriptive study. *BMJ* 2014; 348: g3555.
- 36 EMA. Article 20 referral, HPV vaccines - ASK-20823 - Decision letter to the requester - confirmatory application. 2016 July 11.

- 37 Wikipedia. Duilio Poggiolini. Available online at: http://en.wikipedia.org/wiki/Duilio_Poggiolini (accessed 10 November 2012).
- 38 Abbott A. Italian health sector in disarray following more scandals. *Nature* 1993; 364: 663.
- 39 Day M. Italian police arrest drug officials over alleged falsification of data. *BMJ* 2008; 336: 1208–9.
- 40 Flere vælger HPV-vaccine fra - flere vil dø af livmoderkræft. *BT* 2016 May 6.
- 41 Ioannidis JPA, Evans SJW, Gøtzsche PC, O'Neill RT, Altman DG, Schulz K, Moher D, CONSORT Group. Better Reporting of Harms in Randomized Trials: An Extension of the CONSORT Statement. *Ann Intern Med* 2004; 141: 781-8.
- 42 Jefferson T, Jones MA, Doshi P, Del Mar CB, Hama R, Thompson MJ, Spencer EA, Onakpoya IJ, Mahtani KR, Nunan D, Howick J, Heneghan CJ. Neuraminidase inhibitors for preventing and treating influenza in adults and children. *Cochrane Database of Systematic Reviews* 2014, Issue 4. Art. No.: CD008965.
- 43 Maund E. The effect of selective serotonin reuptake inhibitors (SSRIs) on suicidality and violent behaviour. PhD thesis. University of Copenhagen 2015; June 28: pages 89-90. Available from: <http://nordic.cochrane.org/research-highlights>.
- 44 [Hearing in the Danish Parliament about the safety of HPV vaccines]. Dec 17, 2005. <http://www.ft.dk/webtv/video/20151/suu/tv.3040.aspx?i=2015-12-17T15>.
- 45 Anderson H. Is HPV vaccine safe? Hainault mum says daughter's chronic fatigue is linked to cancer drug. *Ilford Recorder* 2015 Sept 24.
- 46 Guido Rasi. EMA Public Declaration of Interests. 20 July 2015. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123382.pdf.
- 47 Guido Rasi's patents. <http://patents.justia.com/search?q=guido+rasi> (downloaded 7 May 2016).
- 48 Decision on rules relating to Articles 11a and 13 of the Staff Regulations concerning the handling of declared interests of employees of the European Medicines Agency. 1 February 2012. EMA/MB/500408/2011.
- 49 Garattini S. The European Medicines Agency is still too close to industry: Two decades after its inception, the agency still fails to put patients' interests first. *BMJ* 2016; 353: i2412.

Appendix. Correspondence related to the declaration of interests for the EMA's executive director

As noted above on page 50, we believe this correspondence has considerable public interest and we have therefore decided to include the entire correspondence in the Appendix to this complaint to the ombudsman.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Professor Peter C Gøtsche
Nordic Cochrane Centre
Rigshospitalet, Dept. 7811
Blegdamsvej 9
2100 Copenhagen
DENMARK

17 June 2016
EMA/397114/2016
Deputy Executive Director

Dear Prof Gøtsche

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 relating to maladministration at EMA. This reply only deals with point 4 of the section "Conflicts of interest" and a number of allegations on page 17 in the section "Final remarks" in your complaint letter. A reply to the other issues you have raised in your complaint letter is being finalised and will be provided to you within the next few days.

In your complaint you allege that Prof Rasi may have a conflict of interest, stemming from his previous contacts with industry, and which you claim he failed to declare. Without prejudice to any response and defence that Prof Rasi may wish to forward to you directly, EMA would like to refute your unsubstantiated allegations in the strongest possible terms, for the sake of transparency owed to the general public and to the EU regulatory network of which EMA is an important member.

The Decision on rules relating to Articles 11, 11a and 13 of the Staff Regulations concerning the handling of declared interests of staff members of the European Medicines Agency and candidates before recruitment (EMA/622828/2013(revised)) describes the interests in pharmaceutical industry to be declared by the Agency's staff. Amongst other things, EMA staff members are required to declare in their declaration of interests (DoI) any ownership of a patent held for a period of 5 years prior to the start of employment with the Agency.

As you may be aware (see for instance [European IPR Helpdesk](#)), the inventor mentioned on a patent is the creator of the invention and is always entitled to be designated on the patent, regardless of who files the patent application or owns the patent. An inventor remains an inventor throughout the term of a patent, but he is not necessarily the owner of the patent, e.g. the ownership rights may be vested originally upon, or subsequently assigned to, a subject other than the inventor/s. Only the owner of a patent can enjoy economic rights with regard to that particular invention. Therefore, neither the applicable rules, nor considerations of common sense oblige EMA staff to declare in their DoI any patents for which they are the inventor/s, but not the owner/s, unless the inventor is entitled to financial benefits (e.g. lump-sum or royalties) stemming from the exploitation of the invention.



The same principle is applicable to European experts. According to the EMA policy on the handling of declarations of interests of scientific committees' members and experts (EMA/626261/2014, Corr. 1), the definition of financial interests encompasses intellectual property rights relating to a medicinal product, including patents. An expert is required to declare such an interest if the patent is owned by the individual or if the individual is directly a beneficiary of the exploitation of the patent. If the expert is the inventor of the patent, but not the owner or beneficiary, there is no obligation to declare it.

The Agency's Executive Director Prof Rasi is indeed mentioned on a number of patents, even beyond those referred to in footnote 15 of your complaint letter, but only as inventor, not as owner of the patents. Prof Rasi does not own any patent together with Sigma-Tau. He is named as inventor on 2 patent families for which Sigma-Tau is named as applicant or patentee. He is not even the beneficiary of those patent families. Hence there was and there is no obligation for him to declare these patents in his DoI as EMA staff member in accordance with EMA's proceedings on the handling of DoIs.

We would also like to clarify that Prof Rasi has never worked with or for Sigma-Tau and that no former Sigma-Tau employee joined EMA since 2011 with the exception of Mr S. Marino, who was indeed the former General Counsel at Sigma-Tau, as publicly announced by EMA when he was hired after a very rigorous competition run by a selection panel featuring also external members from the Legal Service of the European Commission. Prof Rasi was not part of that selection panel and he did not know Mr Marino when he was still working in industry. The statements appearing at page 17 of the Nordic Cochrane complaint against EMA have therefore no foundation.

We trust that the information provided in this letter has adequately addressed the points raised in your complaint letter. Taking into account the seriousness of the accusations made via the Internet and the echo that these allegations have had worldwide, EMA reserves the right to protect its reputation through all appropriate means. Please also note that EMA will publish this reply for the sake of transparency.

Yours sincerely,

[Signature on File]

Noël Wathion
Deputy Executive Director

CC: Karsten Juhl Jørgensen, Deputy Director of the Nordic Cochrane Centre, Rigshospitalet
Tom Jefferson, Honorary Research Fellow, Centre for Evidence Based Medicine, Oxford OX2 6GG
Margrete Auken, MEP (The Greens/European Free Alliance)
Louise Brinth, PhD, MD, Danish Syncope Unit, Frederiksberg

Direct Email: adam.tudor@carter-ruck.com
Direct Fax: 020 7353 5553

Our Ref: AT/MP/16091.1
Your Ref: EMA/408257/2016

8 July 2016

BY EMAIL & POST pcg@cochrane.dk

PRIVATE AND CONFIDENTIAL

Professor Peter C. Gøtzsche
Nordic Cochrane Centre
Rigshospitalet, Dept. 7811
Blegsdamsvej 9
2100 Copenhagen
Denmark

COPY

Carter-Ruck

Dear Sir

Our Client: Professor Guido Rasi

We act for Professor Guido Rasi, the Executive Director at the London-based European Medicines Agency ("EMA").

Our client has consulted us in relation to certain aspects of a document entitled "*Complaint to the European Medicines Agency (EMA) over maladministration at the EMA*" ("the Publication"), which was published on 26 May 2016 under the banner of the Nordic Cochrane Centre and sent in your name, along with those of a number of co-signatories.

We wish to make clear at the outset that it is not the purpose of this letter to address those parts of the Publication concerning Nordic Cochrane's critique of EMA in the context of the latter's Assessment Report of November 2016; we are aware that those matters have been addressed with you by EMA itself in its letter of 1 July 2016.

However, the Publication contains certain discrete statements (specifically on pages 15 and 17) which are highly defamatory of our client individually, alleging, as they will have been understood to do:-

- That Professor Rasi has, in breach of his ethical and legal obligations, failed to declare his interest in various registered patents.
- That, acting in brazen conflict of interest and contrary to the basic principles of transparency and propriety in a public institution such as the EMA, Professor Rasi recruited a number of individuals, including Stefano Marino, from Sigma Tau – a company with which (according to the Publication) he has worked for many years and with which he has close ongoing commercial interests in the form of patents.
- That in consequence Mr Marino, far from securing his role at EMA through proper and transparent means and solely on merit, is strongly to be suspected of having benefited from nepotism and improper patronage on the part of Professor Rasi.

As well as being defamatory of our client, these allegations are also wholly untrue.

We are informed that Noël Wathion of the EMA wrote to you on 17 June 2016, explaining in detail the baselessness of these allegations. Despite the gravity of those allegations, the EMA has not received so much as an acknowledgement of Mr

PCRI-2109366.1

Carter-Ruck Solicitors

6 St Andrew Street
London EC4A 3AE

T 020 7353 5005
F 020 7353 5553
DX 333 Chancery Lane
www.carter-ruck.com

Partners

Alasdair Pepper
Guy Martin
Nigel Tait
Ruth Collard
Cameron Doley
Claire Gill
Adam Tudor
Isabel Martorell

Partnership Secretary

Helen Burrluck

Authorised and regulated
by the Solicitors Regulation
Authority

SRA No. 44769

Wathion's letter, let alone any substantive response or suitable retraction and correction.

We do not propose in this letter to repeat in detail what was said in Mr Wathion's letter, a copy of which we attach for your further reference. Suffice it to say that there is simply no basis for alleging that Professor Rasi has in any way failed to comply with his obligation to declare interests.

It is clear that in publishing these false allegations concerning Professor Rasi, you failed to properly scrutinise the applicable EMA policies and rules on declarations of interest, or to understand the basic technicalities and nomenclature of patent registration. Had you done so (or had you taken the trouble to contact Professor Rasi before publishing these serious misstatements) then you would have been aware that, while Professor Rasi has indeed been listed on a number of patent registrations within the past five years, that is solely as an inventor, not as owner.

While the inventor will always be listed in the registration material throughout the period of the patent, it certainly does not automatically follow that he or she is the owner of the patent or might in any way benefit from it financially. Thus, in Professor Rasi's case, he has never, and does not, have any economic rights or financial interest or benefit (whether actual or potential) in, or arising from, any of the patents to which the Publication refers.

That being the case, Professor Rasi was and is not under any obligation to declare his status as a mere inventor of certain patents in his EMA declaration of interests; indeed it would make no sense for him to do so.

To make matters worse, in the penultimate paragraph on page 17 of the Publication, you clearly seek to suggest that, acting in flagrant conflict of interest (if not corruptly) Professor Rasi "brought in" (ie recruited) "a number of people", including Mr Marino, from Sigma Tau – a company with whom, you suggest, Professor Rasi has or has had a commercial relationship.

Once again, these allegations are completely unfounded. As Mr Wathion has already made clear and as we have alluded to above, Professor Rasi does not "own any patents with" Sigma Tau. He is registered simply as an inventor in respect of two patent families of which Sigma Tau was applicant or patentee. He has no financial or other interest (whether actual or potential) in these patents. Nor has Professor Rasi ever "worked with" Sigma Tau, as you assert.

It is similarly untrue for you to assert that Professor Rasi "brought in" people from Sigma Tau. We note in passing that, while casting this (false) aspersion in general terms, the Publication does not cite any name other than Mr Marino. Yet, as Mr Wathion has already made clear, Professor Rasi played no part whatsoever in the selection or recruitment of Mr Marino or indeed anyone else from Sigma Tau; indeed, Professor Rasi did not even know Mr Marino when he was working at that company. Mr Marino was recruited entirely on merit and in accordance with the relevant procedures; for you to suggest otherwise is as false as it is damaging to the professional reputations both of Professor Rasi and Mr Marino.

As you will appreciate, the publication of these serious, yet wholly false, allegations is extremely damaging to our client's professional and personal reputation, going to the heart of his integrity and unjustifiably casting doubt on his compliance with his legal obligations and on his professionalism and ethics. Similarly, Mr Marino is a lawyer of some 30 years' standing; for a body such as Nordic Cochrane to (falsely) impute that he secured his current role through questionable and quite possibly corrupt means, is wholly unjustified and highly damaging.

Our client has asked us to stress that he recognises and respects the importance of NGOs such as Nordic Cochrane being free to subject to scrutiny and call to account the activities of public authorities such as the EMA and other bodies performing an

important role in public health, provided those criticisms are published reasonably and in good faith. However, there can be no justification whatsoever for publishing serious libels concerning individuals in the manner complained of in this letter, particularly in circumstances where you made no effort whatsoever to put these allegations to our client before publication.

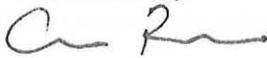
Less justifiable still is your decision to publish these falsehoods to the world online at <http://nordic.cochrane.org/sites/nordic.cochrane.org/files/uploads/ResearchHighlights/Complaint-to-EMA-over-EMA.pdf>, where they will no doubt have been (and, if uncorrected, will in future be) viewed by a large number of individuals worldwide, including in the UK (where our client lives and works, and where EMA and, as we understand it, your umbrella organisation is based). Our client is also concerned to note that the Publication has, inevitably, also been picked up by at least one other website, and which makes specific reference to the personal allegations which are the subject of this letter:

<http://www.activistpost.com/2016/06/prestigious-cochrane-challenges-the-european-medicines-agency-about-hpv-vaccines-harms.html>

We wish to make clear that our client has no wish to become embroiled in a legal dispute, whether with the Nordic Cochrane Centre or with you as the author of the Publication. However, our client hopes that you will appreciate that, such is the seriousness of these allegations, he cannot allow them to go unchallenged or uncorrected. He also hopes that, as a reputable and purportedly responsible organisation, you will agree immediately to amend the relevant passages of the Publication, and to publish (in terms to be agreed) a suitable statement of correction and apology withdrawing these false allegations.

We look forward to hearing from you within 10 days of the date of this letter. In the meantime we must expressly reserve all of our client's rights.

Yours faithfully



Carter-Ruck

Direct Email: adam.tudor@carter-ruck.com
Direct Fax: 020 7353 5553

Our Ref: AT/MP/16091.1
Your Ref: EMA/408257/2016

21 July 2016

BY EMAIL & POST pcg@cochrane.dk

PRIVATE AND CONFIDENTIAL

Professor Peter C. Gøtzsche
Nordic Cochrane Centre
Rigshospitalet, Dept. 7811
Blegsdamsvej 9
2100 Copenhagen Ø,
Denmark

Carter-Ruck

Dear Sir

Our Client: Professor Guido Rasi

We refer to our letter dated 8 July 2016, a further copy of which is enclosed for your ease of reference.

We note that we have not had the courtesy of an acknowledgment of receipt of our letter, still less the substantive response which we had requested be provided by the beginning of this week.

May we please now hear from you in full, without delay.

Yours faithfully



Carter-Ruck

Carter-Ruck Solicitors

6 St Andrew Street
London EC4A 3AE

T 020 7353 5005
F 020 7353 5553
DX 333 Chancery Lane
www.carter-ruck.com

Partners

Alasdair Pepper
Guy Martin
Nigel Tait
Ruth Collard
Cameron Doley
Claire Gill
Adam Tudor
Isabel Martorell

Partnership Secretary

Helen Burrluck

Authorised and regulated
by the Solicitors Regulation
Authority

SRA No. 44769

Direct Email: adam.tudor@carter-ruck.com
Direct Fax: 020 7353 5553

Our Ref: AT/MP/16091.1
Your Ref: EMA/408257/2016

8 July 2016

BY EMAIL & POST pcg@cochrane.dk

PRIVATE AND CONFIDENTIAL

Professor Peter C. Gøtzsche
Nordic Cochrane Centre
Rigshospitalet, Dept. 7811
Blegsdamsvej 9
2100 Copenhagen
Denmark

COPY

Carter-Ruck

Dear Sir

Our Client: Professor Guido Rasi

We act for Professor Guido Rasi, the Executive Director at the London-based European Medicines Agency ("EMA").

Our client has consulted us in relation to certain aspects of a document entitled "*Complaint to the European Medicines Agency (EMA) over maladministration at the EMA*" ("the Publication"), which was published on 26 May 2016 under the banner of the Nordic Cochrane Centre and sent in your name, along with those of a number of co-signatories.

We wish to make clear at the outset that it is not the purpose of this letter to address those parts of the Publication concerning Nordic Cochrane's critique of EMA in the context of the latter's Assessment Report of November 2016; we are aware that those matters have been addressed with you by EMA itself in its letter of 1 July 2016.

However, the Publication contains certain discrete statements (specifically on pages 15 and 17) which are highly defamatory of our client individually, alleging, as they will have been understood to do:-

- That Professor Rasi has, in breach of his ethical and legal obligations, failed to declare his interest in various registered patents.
- That, acting in brazen conflict of interest and contrary to the basic principles of transparency and propriety in a public institution such as the EMA, Professor Rasi recruited a number of individuals, including Stefano Marino, from Sigma Tau – a company with which (according to the Publication) he has worked for many years and with which he has close ongoing commercial interests in the form of patents.
- That in consequence Mr Marino, far from securing his role at EMA through proper and transparent means and solely on merit, is strongly to be suspected of having benefited from nepotism and improper patronage on the part of Professor Rasi.

As well as being defamatory of our client, these allegations are also wholly untrue.

We are informed that Noël Wathion of the EMA wrote to you on 17 June 2016, explaining in detail the baselessness of these allegations. Despite the gravity of those allegations, the EMA has not received so much as an acknowledgement of Mr

PCRI-2109366.1

Carter-Ruck Solicitors

6 St Andrew Street
London EC4A 3AE

T 020 7353 5005
F 020 7353 5553
DX 333 Chancery Lane
www.carter-ruck.com

Partners

Alasdair Pepper
Guy Martin
Nigel Tait
Ruth Collard
Cameron Doley
Claire Gill
Adam Tudor
Isabel Martorell

Partnership Secretary

Helen Burrluck

Authorised and regulated
by the Solicitors Regulation
Authority

SRA No. 44769

Wathion's letter, let alone any substantive response or suitable retraction and correction.

We do not propose in this letter to repeat in detail what was said in Mr Wathion's letter, a copy of which we attach for your further reference. Suffice it to say that there is simply no basis for alleging that Professor Rasi has in any way failed to comply with his obligation to declare interests.

It is clear that in publishing these false allegations concerning Professor Rasi, you failed to properly scrutinise the applicable EMA policies and rules on declarations of interest, or to understand the basic technicalities and nomenclature of patent registration. Had you done so (or had you taken the trouble to contact Professor Rasi before publishing these serious misstatements) then you would have been aware that, while Professor Rasi has indeed been listed on a number of patent registrations within the past five years, that is solely as an inventor, not as owner.

While the inventor will always be listed in the registration material throughout the period of the patent, it certainly does not automatically follow that he or she is the owner of the patent or might in any way benefit from it financially. Thus, in Professor Rasi's case, he has never, and does not, have any economic rights or financial interest or benefit (whether actual or potential) in, or arising from, any of the patents to which the Publication refers.

That being the case, Professor Rasi was and is not under any obligation to declare his status as a mere inventor of certain patents in his EMA declaration of interests; indeed it would make no sense for him to do so.

To make matters worse, in the penultimate paragraph on page 17 of the Publication, you clearly seek to suggest that, acting in flagrant conflict of interest (if not corruptly) Professor Rasi "brought in" (ie recruited) "a number of people", including Mr Marino, from Sigma Tau – a company with whom, you suggest, Professor Rasi has or has had a commercial relationship.

Once again, these allegations are completely unfounded. As Mr Wathion has already made clear and as we have alluded to above, Professor Rasi does not "own any patents with" Sigma Tau. He is registered simply as an inventor in respect of two patent families of which Sigma Tau was applicant or patentee. He has no financial or other interest (whether actual or potential) in these patents. Nor has Professor Rasi ever "worked with" Sigma Tau, as you assert.

It is similarly untrue for you to assert that Professor Rasi "brought in" people from Sigma Tau. We note in passing that, while casting this (false) aspersion in general terms, the Publication does not cite any name other than Mr Marino. Yet, as Mr Wathion has already made clear, Professor Rasi played no part whatsoever in the selection or recruitment of Mr Marino or indeed anyone else from Sigma Tau; indeed, Professor Rasi did not even know Mr Marino when he was working at that company. Mr Marino was recruited entirely on merit and in accordance with the relevant procedures; for you to suggest otherwise is as false as it is damaging to the professional reputations both of Professor Rasi and Mr Marino.

As you will appreciate, the publication of these serious, yet wholly false, allegations is extremely damaging to our client's professional and personal reputation, going to the heart of his integrity and unjustifiably casting doubt on his compliance with his legal obligations and on his professionalism and ethics. Similarly, Mr Marino is a lawyer of some 30 years' standing; for a body such as Nordic Cochrane to (falsely) impute that he secured his current role through questionable and quite possibly corrupt means, is wholly unjustified and highly damaging.

Our client has asked us to stress that he recognises and respects the importance of NGOs such as Nordic Cochrane being free to subject to scrutiny and call to account the activities of public authorities such as the EMA and other bodies performing an

important role in public health, provided those criticisms are published reasonably and in good faith. However, there can be no justification whatsoever for publishing serious libels concerning individuals in the manner complained of in this letter, particularly in circumstances where you made no effort whatsoever to put these allegations to our client before publication.

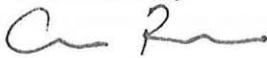
Less justifiable still is your decision to publish these falsehoods to the world online at <http://nordic.cochrane.org/sites/nordic.cochrane.org/files/uploads/ResearchHighlights/Complaint-to-EMA-over-EMA.pdf>, where they will no doubt have been (and, if uncorrected, will in future be) viewed by a large number of individuals worldwide, including in the UK (where our client lives and works, and where EMA and, as we understand it, your umbrella organisation is based). Our client is also concerned to note that the Publication has, inevitably, also been picked up by at least one other website, and which makes specific reference to the personal allegations which are the subject of this letter:

<http://www.activistpost.com/2016/06/prestigious-cochrane-challenges-the-european-medicines-agency-about-hpv-vaccines-harms.html>

We wish to make clear that our client has no wish to become embroiled in a legal dispute, whether with the Nordic Cochrane Centre or with you as the author of the Publication. However, our client hopes that you will appreciate that, such is the seriousness of these allegations, he cannot allow them to go unchallenged or uncorrected. He also hopes that, as a reputable and purportedly responsible organisation, you will agree immediately to amend the relevant passages of the Publication, and to publish (in terms to be agreed) a suitable statement of correction and apology withdrawing these false allegations.

We look forward to hearing from you within 10 days of the date of this letter. In the meantime we must expressly reserve all of our client's rights.

Yours faithfully



Carter-Ruck



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Professor Peter C Gøtsche
Nordic Cochrane Centre
Rigshospitalet, Dept. 7811
Blegdamsvej 9
2100 Copenhagen
DENMARK

17 June 2016
EMA/397114/2016
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 relating to maladministration at EMA. This reply only deals with point 4 of the section "Conflicts of interest" and a number of allegations on page 17 in the section "Final remarks" in your complaint letter. A reply to the other issues you have raised in your complaint letter is being finalised and will be provided to you within the next few days.

In your complaint you allege that Prof Rasi may have a conflict of interest, stemming from his previous contacts with industry, and which you claim he failed to declare. Without prejudice to any response and defence that Prof Rasi may wish to forward to you directly, EMA would like to refute your unsubstantiated allegations in the strongest possible terms, for the sake of transparency owed to the general public and to the EU regulatory network of which EMA is an important member.

The Decision on rules relating to Articles 11, 11a and 13 of the Staff Regulations concerning the handling of declared interests of staff members of the European Medicines Agency and candidates before recruitment (EMA/622828/2013(revised)) describes the interests in pharmaceutical industry to be declared by the Agency's staff. Amongst other things, EMA staff members are required to declare in their declaration of interests (DoI) any ownership of a patent held for a period of 5 years prior to the start of employment with the Agency.

As you may be aware (see for instance [European IPR Helpdesk](#)), the inventor mentioned on a patent is the creator of the invention and is always entitled to be designated on the patent, regardless of who files the patent application or owns the patent. An inventor remains an inventor throughout the term of a patent, but he is not necessarily the owner of the patent, e.g. the ownership rights may be vested originally upon, or subsequently assigned to, a subject other than the inventor/s. Only the owner of a patent can enjoy economic rights with regard to that particular invention. Therefore, neither the applicable rules, nor considerations of common sense oblige EMA staff to declare in their DoI any patents for which they are the inventor/s, but not the owner/s, unless the inventor is entitled to financial benefits (e.g. lump-sum or royalties) stemming from the exploitation of the invention.



The same principle is applicable to European experts. According to the EMA policy on the handling of declarations of interests of scientific committees' members and experts (EMA/626261/2014, Corr. 1), the definition of financial interests encompasses intellectual property rights relating to a medicinal product, including patents. An expert is required to declare such an interest if the patent is owned by the individual or if the individual is directly a beneficiary of the exploitation of the patent. If the expert is the inventor of the patent, but not the owner or beneficiary, there is no obligation to declare it.

The Agency's Executive Director Prof Rasi is indeed mentioned on a number of patents, even beyond those referred to in footnote 15 of your complaint letter, but only as inventor, not as owner of the patents. Prof Rasi does not own any patent together with Sigma-Tau. He is named as inventor on 2 patent families for which Sigma-Tau is named as applicant or patentee. He is not even the beneficiary of those patent families. Hence there was and there is no obligation for him to declare these patents in his DoI as EMA staff member in accordance with EMA's proceedings on the handling of DoIs.

We would also like to clarify that Prof Rasi has never worked with or for Sigma-Tau and that no former Sigma-Tau employee joined EMA since 2011 with the exception of Mr S. Marino, who was indeed the former General Counsel at Sigma-Tau, as publicly announced by EMA when he was hired after a very rigorous competition run by a selection panel featuring also external members from the Legal Service of the European Commission. Prof Rasi was not part of that selection panel and he did not know Mr Marino when he was still working in industry. The statements appearing at page 17 of the Nordic Cochrane complaint against EMA have therefore no foundation.

We trust that the information provided in this letter has adequately addressed the points raised in your complaint letter. Taking into account the seriousness of the accusations made via the Internet and the echo that these allegations have had worldwide, EMA reserves the right to protect its reputation through all appropriate means. Please also note that EMA will publish this reply for the sake of transparency.

Yours sincerely,

[Signature on File]

Noël Wathion
Deputy Executive Director

CC: Karsten Juhl Jørgensen, Deputy Director of the Nordic Cochrane Centre, Rigshospitalet
Tom Jefferson, Honorary Research Fellow, Centre for Evidence Based Medicine, Oxford OX2 6GG
Margrete Auken, MEP (The Greens/European Free Alliance)
Louise Brinth, PhD, MD, Danish Syncope Unit, Frederiksberg

1 August 2016

To Carter-Ruck Solicitors

you have sent me two emails, on 8 and 21 July, and wrote in the one from 21 July:

We note that we have not had the courtesy of an acknowledgment of receipt of our letter, still less the substantive response which we had requested be provided by the beginning of this week.

July and August are holiday season. This is my first work day after 4 weeks holidays in July, so I have not had any chance of reacting to your emails before today, as I have not seen them.

We shall respond as soon as we can.

bw

Peter Gøtzsche

Direct Email: adam.tudor@carter-ruck.com
Direct Fax: 020 7353 5553

Our Ref: AT/MP/16091.1
Your Ref: EMA/408257/2016

2 August 2016

BY EMAIL & POST pcg@cochrane.dk

PRIVATE AND CONFIDENTIAL

Professor Peter C. Gøtzsche
Nordic Cochrane Centre
Rigshospitalet, Dept. 7811
Blegsdamsvej 9
2100 Copenhagen Ø,
Denmark

Carter-Ruck

Dear Sir

Our Client: Professor Guido Rasi

We refer to your email of yesterday's date.

We note your comments regarding the holiday period and look forward to hearing from you now without further delay, and in any event within ten days of the date of this letter.

Yours faithfully

Carter-Ruck

Carter-Ruck

Carter-Ruck Solicitors

6 St Andrew Street
London EC4A 3AE

T 020 7353 5005
F 020 7353 5553
DX 333 Chancery Lane
www.carter-ruck.com

Partners

Alasdair Pepper
Guy Martin
Nigel Tait
Ruth Collard
Cameron Doley
Claire Gill
Adam Tudor
Isabel Martorell

Partnership Secretary

Helen Burrluck

Authorised and regulated
by the Solicitors Regulation
Authority

SRA No. 44769

12 August 2016

Dear Carter-Ruck solicitors,

In your letter from 8 July, you write that “Despite the gravity of those allegations [about conflicts of interest], the EMA has not received so much as an acknowledgement of Mr Wathion's letter, let alone any substantive response or suitable retraction and correction.”

The reason why we did not respond to this particular letter is that we raised several other conflicts of interest issues than those related to your client, Professor Guido Rasi, and we therefore awaited the EMA's response to our letter in its entirety. Mr Wathion wrote to us in his letter from 17 June: “A reply to the other issues you have raised in your complaint letter is being finalised and will be provided to you within the next few days.” We therefore preferred to wait a few days before we responded in toto. As it turned out, however, the EMA's response was not sent in a “few days”, but in July when I was on holiday, so I had no opportunity of responding.

You also write that Rasi hopes that we will agree “to amend the relevant passages of the Publication, and to publish (in terms to be agreed) a suitable statement of correction and apology withdrawing these false allegations.”

As researchers, we believe it would be wrong to change published documents. If errors are detected in scientific papers, the papers are not changed but errata are published separately. We have therefore written a separate document, which we will publish on the Nordic Cochrane Centre's website, alongside our complaint to the EMA from 26 May.

We hope we have thereby met the wishes of Prof. Rasi. See our corrections attached.

bw

Peter C Gøtzsche
on behalf of all authors

12 August 2016

Corrections of conflicts of interest issues in our
[“Complaint to the European Medicines Agency \(EMA\) over maladministration at the EMA”](#) from 26
May 2016.

We have been made aware that we have misinterpreted some of the information that was available to us in relation to conflicts of interest issues and we therefore make corrections here.

About the EMAs executive director, we wrote:

“We noticed a Guido Rasi’s name associated with patents for inventions and wonder whether this is the same person who is the EMA’s director. If so, we believe Rasi has failed to declare his conflicts of interest.”

“a Guido Rasi, which we assume is the same person, holds a number of patents, some of which were filed or approved in 2012 or 2013, and where the applicant was a drug company (Applicant: SciClone Pharmaceuticals, Inc.; Inventors: Guido Rasi, Enrico Garaci, Francesco Bistoni, Luigina Romani, Paolo Di Francesco) (15). As they go back less than five years, we believe he should have declared them, according to the EMA’s regulations concerning the handling of declared interests of its employees (16).”

“the EMA’s director, Guido Rasi, has brought in a number of people from the drug company Sigma Tau that include Stefano Marino, his head of legal affairs. Rasi has worked with this company for many years and apparently owns several patents together with the company (15).”

“the EMA’s director, Guido Rasi, declared on 20 July 2015 that he had no conflicts of interest (14). On a form called ‘EMA Public Declaration of Interests,’ he replied ‘none’ to all four questions, also to question 4, which is: ‘Other interests or facts whether or not related to the pharmaceutical industry⁴ which you consider should be made known to the Agency and the public, including matter relating to members of your household⁵.’”

The EMAs deputy executive director, Noël Wathion, has informed us that:

“EMA staff members are required to declare in their declaration of interests (DoI) any ownership of a patent held for a period of 5 years prior to the start of employment with the Agency.”

“the inventor mentioned on a patent is the creator of the invention and is always entitled to be designated on the patent, regardless of who files the patent application or owns the patent. An inventor remains an inventor throughout the term of a patent, but he is not necessarily the owner of the patent, e.g. the ownership rights may be vested originally upon, or subsequently assigned to, a

subject other than the inventor/s. Only the owner of a patent can enjoy economic rights with regard to that particular invention. Therefore, neither the applicable rules, nor considerations of common sense oblige EMA staff to declare in their DoI any patents for which they are the inventor/s, but not the owner/s, unless the inventor is entitled to financial benefits (e.g. lump-sum or royalties) stemming from the exploitation of the invention.”

“The Agency’s Executive Director Prof Rasi is indeed mentioned on a number of patents, even beyond those referred to in footnote 15 of your complaint letter, but only as inventor, not as owner of the patents. Prof Rasi does not own any patent together with Sigma-Tau. He is named as inventor on 2 patent families for which Sigma-Tau is named as applicant or patentee. He is not even the beneficiary of those patent families. Hence there was and there is no obligation for him to declare these patents in his DoI as EMA staff member in accordance with EMA’s proceedings on the handling of DoIs.”

“We would also like to clarify that Prof Rasi has never worked with or for Sigma-Tau and that no former Sigma-Tau employee joined EMA since 2011 with the exception of Mr S. Marino, who was indeed the former General Counsel at Sigma-Tau, as publicly announced by EMA when he was hired after a very rigorous competition run by a selection panel featuring also external members from the Legal Service of the European Commission. Prof Rasi was not part of that selection panel and he did not know Mr Marino when he was still working in industry. The statements appearing at page 17 of the Nordic Cochrane complaint against EMA have therefore no foundation.”

Our comment:

We apologize for the mistakes. We were not aware of the legal subtleties and assumed that an inventor of a patented technology is also an owner of that patent, as it is highly unusual that inventors give away their patents to drug companies without benefiting from them and without having any working relationship with that particular company.

As concerns the employment of people, there are legal procedures to follow, but it is also very common that the employer contacts people informally, encouraging them to apply for the post.

About the EMA’s rapporteur, we wrote:

“We also believe that the rapporteur for the EMA’s report, Julie Williams (2), has failed to declare her conflicts of interest.”

We apologize for this mistake, which stems from the limited information that was available to us. In the material from the EMA that we had acquired, we could not see where this person worked and therefore looked her up on the Internet. Unfortunately, we found the wrong person, another Professor Julie Williams. Therefore, what we wrote about Julie Williams in our complaint to the EMA should be disregarded, apart from this sentence, which is correct:

“in Williams’ ‘Public declaration of interests’ on the EMA’s homepage from 21 November 2015 (13), no conflicts of interest are declared.”

Sincerely,

A handwritten signature in blue ink, appearing to read 'P. Gøtzsche', with a stylized, cursive script.

Peter C Gøtzsche, DrMedSci, MSc
Director of the Nordic Cochrane Centre, Rigshospitalet
Professor, University of Copenhagen

Co-signatures:

Karsten Juhl Jørgensen, Deputy Director of the Nordic Cochrane Centre, Rigshospitalet

Tom Jefferson, Honorary Research Fellow, Centre for Evidence Based Medicine, Oxford OX2 6GG,
United Kingdom

Margrete Auken, MEP (The Greens/European Free Alliance)

Louise Brinth, PhD, MD, Danish Syncope Unit, Frederiksberg

Direct Email: adam.tudor@carter-ruck.com
Direct Fax: 020 7353 5553

Our Ref: AT/MP/16091.1
Your Ref: EMA/408257/2016

18 August 2016

BY EMAIL & POST pcg@cochrane.dk

PRIVATE AND CONFIDENTIAL

Professor Peter C. Gøtzsche
Nordic Cochrane Centre
Rigshospitalet, Dept. 7811
Blegdamsvej 9
2100 Copenhagen Ø,
Denmark

Carter-Ruck

Dear Sir

Our Client: Professor Guido Rasi

We refer to your email dated 12 August.

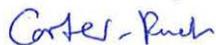
Our client is prepared to accept your proposal of a separate errata document, to be published on the Nordic Cochrane Centre's website, alongside your original complaint to the EMA from 26 May.

The current wording of the document is however not acceptable to our client. We enclose a revised version, in which our amendments are highlighted, which we trust is uncontroversial.

Please confirm this version of the wording is now agreed, and that the errata document will be published online by no later than close of business on **Friday 26 August**.

We look forward to hearing from you.

Yours faithfully



Carter-Ruck

Carter - Ruck Solicitors

6 St Andrew Street
London EC4A 3AE

T 020 7353 5005

F 020 7353 5553

DX 333 Chancery Lane

www.carter-ruck.com

Partners

Alasdair Pepper

Guy Martin

Nigel Tait

Ruth Collard

Cameron Doley

Claire Gill

Adam Tudor

Isabel Martorell

Partnership Secretary

Helen Burrluck

Authorised and regulated
by the Solicitors Regulation
Authority

SRA No. 44769

12 August 2016

Corrections of conflicts of interest issues in our

[“Complaint to the European Medicines Agency \(EMA\) over maladministration at the EMA”](#) from 26 May 2016.

We have been made aware that we have misinterpreted some of the information that was available to us in relation to conflicts of interest issues and we therefore make corrections here.

About the EMAs executive director, we wrote:

“We noticed a Guido Rasi’s name associated with patents for inventions and wonder whether this is the same person who is the EMA’s director. If so, we believe Rasi has failed to declare his conflicts of interest.”

“a Guido Rasi, which we assume is the same person, holds a number of patents, some of which were filed or approved in 2012 or 2013, and where the applicant was a drug company (Applicant: SciClone Pharmaceuticals, Inc.; Inventors: Guido Rasi, Enrico Garaci, Francesco Bistoni, Luigina Romani, Paolo Di Francesco) (15). As they go back less than five years, we believe he should have declared them, according to the EMA’s regulations concerning the handling of declared interests of its employees (16).”

“the EMA’s director, Guido Rasi, has brought in a number of people from the drug company Sigma Tau that include Stefano Marino, his head of legal affairs. Rasi has worked with this company for many years and apparently owns several patents together with the company (15).”

“the EMA’s director, Guido Rasi, declared on 20 July 2015 that he had no conflicts of interest (14). On a form called ‘EMA Public Declaration of Interests,’ he replied ‘none’ to all four questions, also to question 4, which is: ‘Other interests or facts whether or not related to the pharmaceutical industry⁴ which you consider should be made known to the Agency and the public, including matter relating to members of your household⁵.’”

The EMAs deputy executive director, Noël Wathion, has informed us that:

“EMA staff members are required to declare in their declaration of interests (DoI) any ownership of a patent held for a period of 5 years prior to the start of employment with the Agency.”

“the inventor mentioned on a patent is the creator of the invention and is always entitled to be designated on the patent, regardless of who files the patent application or owns the patent. An inventor remains an inventor throughout the term of a patent, but he is not necessarily the owner of the patent, e.g. the ownership rights may be vested originally upon, or subsequently assigned to, a

subject other than the inventor/s. Only the owner of a patent can enjoy economic rights with regard to that particular invention. Therefore, neither the applicable rules, nor considerations of common sense oblige EMA staff to declare in their DoI any patents for which they are the inventor/s, but not the owner/s, unless the inventor is entitled to financial benefits (e.g. lump-sum or royalties) stemming from the exploitation of the invention.”

“The Agency’s Executive Director Prof Rasi is indeed mentioned on a number of patents, even beyond those referred to in footnote 15 of your complaint letter, but only as inventor, not as owner of the patents. Prof Rasi does not own any patent together with Sigma-Tau. He is named as inventor on 2 patent families for which Sigma-Tau is named as applicant or patentee. He is not even the beneficiary of those patent families. Hence there was and there is no obligation for him to declare these patents in his DoI as EMA staff member in accordance with EMA’s proceedings on the handling of DoIs.”

“We would also like to clarify that Prof Rasi has never worked with or for Sigma-Tau and that no former Sigma-Tau employee joined EMA since 2011 with the exception of Mr S. Marino, who was indeed the former General Counsel at Sigma-Tau, as publicly announced by EMA when he was hired after a very rigorous competition run by a selection panel featuring also external members from the Legal Service of the European Commission. Prof Rasi was not part of that selection panel and he did not know Mr Marino when he was still working in industry. The statements appearing at page 17 of the Nordic Cochrane complaint against EMA have therefore no foundation.”

Our comment:

We apologize to Professor Rasi and Stefano Marino for our the mistakes.

We were not aware of the legal subtleties and assumed that an inventor of a patented technology is also an owner of that patent. Professor Rasi has explained to us, and we accept, that this is not correct in his case. , as it is highly unusual that inventors give away their patents to drug companies without benefiting from them and without having any working relationship with that particular company.

As concerns the employment of people, EMA has confirmed, and we accept, that Professor Rasi did not bring anyone to EMA from Sigma-Tau. We acknowledge that Stefano Marino worked previously at Sigma-Tau, but was recruited according to the ordinary, rigorous EU selection procedures and received no favourable treatment at all. there are legal procedures to follow, but it is also very common that the employer contacts people informally, encouraging them to apply for the post.

About the EMA’s rapporteur, we wrote:

“We also believe that the rapporteur for the EMA’s report, Julie Williams (2), has failed to declare her conflicts of interest.”

We apologize to Doctor Julie Williams and EMA for this mistake, which stems from the limited information that was available to us. In the material from the EMA that we had acquired, we could not see where this person worked and therefore looked her up on the Internet. Unfortunately, we

found the wrong person, another Professor Julie Williams. Therefore, what we wrote about Julie Williams in our complaint to the EMA should be disregarded, apart from this sentence, which is correct:

“in Williams’ ‘Public declaration of interests’ on the EMA’s homepage from 21 November 2015 (13), no conflicts of interest are declared.”

Sincerely,



Peter C Gøtzsche, DrMedSci, MSc
Director of the Nordic Cochrane Centre, Rigshospitalet
Professor, University of Copenhagen

Co-signatures:

Karsten Juhl Jørgensen, Deputy Director of the Nordic Cochrane Centre, Rigshospitalet

Tom Jefferson, Honorary Research Fellow, Centre for Evidence Based Medicine, Oxford OX2 6GG,
United Kingdom

Margrete Auken, MEP (The Greens/European Free Alliance)

Louise Brinth, PhD, MD, Danish Syncope Unit, Frederiksberg

23 August 2016

We enclose our comments to your letter from 18 August where we suggest a compromise, which we trust is uncontroversial.

bw

Peter Gøtzsche on behalf of all authors

23 August 2016

Corrections of conflicts of interest issues in our
[“Complaint to the European Medicines Agency \(EMA\) over maladministration at the EMA”](#) from 26 May 2016.

Referring to your letter from 18 August, we are pleased that your client accepts that we publish a separate errata document on the Nordic Cochrane Centre's website, alongside our original complaint to the EMA from 26 May.

You say that the current wording of the document is not acceptable to your client and you have sent suggested amendments, which you ask us to accept.

You highlighted in our document your suggested amendments in red and by using overstrike. The first paragraph just below, which is included in our suggested correction document, was sent to us by the EMAs deputy executive director, Noël Wathion:

“We would also like to clarify that Prof Rasi has never worked with or for Sigma-Tau and that no former Sigma-Tau employee joined EMA since 2011 with the exception of Mr S. Marino, who was indeed the former General Counsel at Sigma-Tau, as publicly announced by EMA when he was hired after a very rigorous competition run by a selection panel featuring also external members from the Legal Service of the European Commission. Prof Rasi was not part of that selection panel and he did not know Mr Marino when he was still working in industry. The statements appearing at page 17 of the Nordic Cochrane complaint against EMA have therefore no foundation.”

We apologize to Professor Rasi and Stefano Marino for our the mistakes.

We were not aware of the legal subtleties and assumed that an inventor of a patented technology is also an owner of that patent. Professor Rasi has explained to us, and we accept, that this is not correct in his case. ~~as it is highly unusual that inventors give away their patents to drug companies without benefiting from them and without having any working relationship with that particular company.~~

As concerns the employment of people, EMA has confirmed, and we accept, that Professor Rasi did not bring anyone to EMA from Sigma-Tau. We acknowledge that Stefano Marino worked previously at Sigma-Tau, but was recruited according to the ordinary, rigorous EU selection procedures and received no favourable treatment at all. ~~there are legal procedures to follow, but it is also very common that the employer contacts people informally, encouraging them to apply for the post.~~

About the EMA's rapporteur, we wrote:

“We also believe that the rapporteur for the EMA's report, Julie Williams (2), has failed to declare her conflicts of interest.”

We apologize to Doctor Julie Williams and EMA for this mistake

Our comments to your suggested amendments

An apology is a very personal thing, and in our opinion the person asking for an apology should not require a particular text or format, as the apology would then not be genuine. We are prepared, however, to take your suggested amendments into consideration.

As it was already clear in our document to whom we address our apologies, there is no need to mention the names again. It is also clear from your own text, which we inserted just above our apologies, what the apologies are about and there is therefore no need to repeat this as part of our apologies. However, to accommodate your wishes, we are willing to do this.

We need to protect our own reputations and therefore need to explain to the readers of this document that our mistakes were made in good faith. Therefore, we cannot accept that you deleted our explanations. We furthermore believe that these explanations are helpful for the readers of this document and therefore have general public interest, and we wish to note that both the EMA and ourselves serve the public interest. Finally, please take into account that four of us are scientists and the fifth is a politician. Being scientists or politicians, we can write what others have told us, making it clear that this is so, but we cannot allow ourselves to be forced to accept statements as fact when we have had no possibility of checking these facts ourselves.

For these reasons, we suggest this compromise, which we trust is uncontroversial:

We apologize for our mistakes.

We were not aware of the legal subtleties and assumed that an inventor of a patented technology is also an owner of that patent, as it is highly unusual that inventors give away their patents to drug companies without benefiting from them and without having any working relationship with that particular company. **Noel Wathion has explained to us that Professor Rasi is not the owner of the patents for which he is named as inventor.**

As concerns the employment of people, there are legal procedures to follow, but it is also very common that the employer contacts people informally, encouraging them to apply for the post. **The EMA has stated to us that Professor Rasi did not bring anyone to EMA from Sigma-Tau and that Stefano Marino was recruited according to the ordinary, rigorous EU selection procedures and received no favourable treatment at all.**

About the EMA's rapporteur, we wrote:

"We also believe that the rapporteur for the EMA's report, Julie Williams (2), has failed to declare her conflicts of interest."

We apologize for this mistake

Sincerely,

A handwritten signature in blue ink, appearing to read 'P. Gøtzsche', with a stylized, cursive script.

Peter C Gøtzsche, DrMedSci, MSc
Director of the Nordic Cochrane Centre, Rigshospitalet
Professor, University of Copenhagen

Co-signatures:

Karsten Juhl Jørgensen, Deputy Director of the Nordic Cochrane Centre, Rigshospitalet

Tom Jefferson, Honorary Research Fellow, Centre for Evidence Based Medicine, Oxford OX2 6GG,
United Kingdom

Margrete Auken, MEP (The Greens/European Free Alliance)

Louise Brinth, PhD, MD, Danish Syncope Unit, Frederiksberg

At 12:40 24-08-2016, Helena Shipman wrote:

Dear Sir,

We refer to your email below and its attachment.

Our client considers that that the wording of the errata document is most of the way there, albeit it is still not acceptable in its current form. Rather than engage in further protracted correspondence, we propose a telephone discussion to try to resolve any remaining issues. Please confirm if you are amenable to this approach, and if so please let us know when would be convenient.

We look forward to hearing from you.

Yours faithfully,

Carter-Ruck

Carter-Ruck Solicitors

Our reply:

27 August 2016

Dear lawyers

We prefer to communicate in writing.

bw

Peter Gøtzsche
Margrete Auken
Louise Brinth
Tom Jefferson
Karsten Juhl Jørgensen

Direct Email: adam.tudor@carter-ruck.com
Direct Fax: 020 7353 5553

Our Ref: AT/MP/16091.1
Your Ref: EMA/408257/2016

7 September 2016

BY EMAIL & POST pcg@cochrane.dk

PRIVATE AND CONFIDENTIAL

Professor Peter C. Gøtzsche
Nordic Cochrane Centre
Rigshospitalet, Dept. 7811
Blegdamsvej 9
2100 Copenhagen Ø,
Denmark

Carter-Ruck

Dear Sir

Our Client: Professor Guido Rasi

We refer to our previous correspondence in this matter and, most recently, to your emailed letter dated 23 August 2016.

As we observed in our email of 24 August, we are hopeful that the parties are now not far apart.

We set out below our proposed amendments to those contained in your 23 August proposal. You will see that, for your ease of reference, we have shown your amendments in red, and our proposed further changes underlined in black or struck through.

We apologize to Professor Rasi and Stefano Marino for our mistakes.

We were not aware of the legal subtleties and assumed that an inventor of a patented technology is also an owner of that patent, as it is highly unusual that inventors give away their patents to drug companies without benefiting from them and without having any working relationship with that particular company. **Noel Wathion has explained to us that Professor Rasi is not the owner of the patents for which he is named as inventor. On the basis of these assurances we accept that Professor Rasi has never had, and does not have, any economic rights or financial interest or benefit (whether actual or potential) in, or arising from, any of the patents to which the Publication refers.**

As concerns the employment of people, there are legal procedures to follow, but it is also very common that the employer contacts people informally, encouraging them to apply for the post. **However, the EMA has stated to us, and as such we accept, that Professor Rasi did not bring anyone to EMA from Sigma-Tau and that Stefano Marino was recruited according to the ordinary, rigorous EU selection procedures and received no favourable treatment at all.**

We comment as follows:

First, you will note that we have amended to name Professor Rasi and Mr Marino. This is important to our clients and, we believe, entirely reasonable given the personal allegations made against both individuals. In the body of your letter of 23 August (page 2, paragraph 2) you in fact confirmed that you were willing to do this

Carter-Ruck Solicitors

6 St Andrew Street
London EC4A 3AE

T 020 7353 5005

F 020 7353 5553

DX 333 Chancery Lane
www.carter-ruck.com

Partners

Alasdair Pepper

Guy Martin

Nigel Tait

Ruth Collard

Cameron Doley

Claire Gill

Adam Tudor

Isabel Martorell

Partnership Secretary

Helen Burrluck

Authorised and regulated
by the Solicitors Regulation
Authority

SRA No. 44769

but (no doubt inadvertently) omitted it from the amendments, so we trust this will be uncontroversial.

Secondly, while our client is willing to accept your proposal for the paragraph commencing "*We were not aware*", it is essential that this paragraph goes on to make clear that, in consequence, our client has never had any financial benefit. Again, this should be uncontroversial.

You will note that our proposals for the second and third paragraphs below confirm Nordic Cochrane's acceptance of the position as explained to you. In your 23 August letter you state that you "*cannot allow [y]ourselves to be forced to accept statements of fact when [you] have no possibility of checking these facts ourselves*". Leaving aside for a moment the fact that the authors of the offending publication felt able to make these untrue statements of fact in the first place without any proper verification, it is clearly essential, and equitable, that in order to properly correct the record, the statement makes clear Nordic Cochrane's acknowledgment of the true position (or else readers will be likely to consider our clients' statements to be self-serving and therefore not credible). We would hope that, given the assurances provided by both EMA and Professor Rasi and the factual explanation given by us in our capacity as Professor Rasi's solicitors, Nordic Cochrane will, on reflection, be willing to accept those explanations and to make that clear in the statement.

We look forward to hearing from you and hope matters can be resolved without delay.

Yours faithfully



Carter-Ruck

11 September 2016

To Carter-Ruck solicitors

We agree that we are now not far apart.

You have deleted the words “highly” and “very” in your suggested amendment although these words are appropriate. It is not only highly unusual, it is in fact extremely unusual, that inventors give away their patents to a particular drug company - in this case Sigma-Tau - without benefiting from them and without having any working relationship with that particular company. We had never heard of any such cases before but are now told that this is the case for Guido Rasi. Similarly, it is very common that the employer contacts people informally, encouraging them to apply for a vacant post, particularly if that post is important for the institution, and we can see nothing wrong with that. This has nothing to do with nepotism, provided all applicants are treated equally in the subsequent selection procedure. However, since you wish to delete these two words, we will accept this proposal.

We wrote to you, on 23 August: “As it was already clear in our document to whom we address our apologies, there is no need to mention the names again. It is also clear from your own text, which we inserted just above our apologies, what the apologies are about and there is therefore no need to repeat this as part of our apologies. However, to accommodate your wishes, we are willing to do this.”

Thus, we said that we were willing to repeat what the apologies were about, and we also inserted this in the text. In your letter from 7 September, you indicate that we should have said that we were willing to mention the names again, but this was not what we meant and wrote. Allow us to say again that an apology is a very personal thing, and that, in our opinion, the person asking for an apology should not require a particular text or format, as the apology would then not be genuine.

As we have already explained, being scientists or politicians, we can write what others have told us, making it clear that this is what they told us, but we cannot allow ourselves to be forced to accept such statements as fact when we have had no possibility of checking these facts ourselves. As lawyers, you know very well that in court cases, one cannot force people to accept and declare that what others tell them is the truth. Therefore, we cannot accept the following amendments, which you suggested in your letter:

“On the basis of these assurances we accept that Professor Rasi has never had, and does not have, any economic rights or financial interest or benefit (whether actual or potential) in, or arising from, any of the patents to which the Publication refers” and “and as such we accept.”

We accepted to take your suggested amendments into consideration, and we believe we have been very forthcoming in changing the text according to your wishes.

best wishes

Peter Gøtzsche
Margrete Auken
Louise Brinth
Tom Jefferson
Karsten Juhl Jørgensen

Direct Email: adam.tudor@carter-ruck.com
Direct Fax: 020 7353 5553

Our Ref: AT/MP/16091.1
Your Ref: EMA/408257/2016

16 September 2016

BY EMAIL & POST pcg@cochrane.dk

PRIVATE AND CONFIDENTIAL

Professor Peter C. Gøtzsche
Nordic Cochrane Centre
Rigshospitalet, Dept. 7811
Blegdamsvej 9
2100 Copenhagen
Denmark

Carter-Ruck

Dear Sir

Our Client: Professor Guido Rasi

We refer to your email dated 11 September 2016.

We note your agreement to the removal of the words “highly” and “very” from the apology.

Your position on identifying our client and Mr Marino in your email dated 23 August was actually very clear and beyond any possible misunderstanding. Given that you have agreed to name Doctor Julie Williams and EMA in your proposed wording, we trust that you will accord our client and Mr Marino the same treatment. We are not asking a particular text or format of the apology. We certainly welcome your statement that the apology is a personal thing and in fact we are only asking that you simply name the persons to whom the apology is addressed.

In light of your reluctance to accept our client’s assurances and explanations, we propose that they are instead, at the very least, acknowledged. We have therefore set out below a further amendment to what we believe is the final wording of the apology, which we trust should be uncontroversial:

We apologise to Professor Rasi and Stefano Marino for our mistakes.

We were not aware of the legal subtleties and assumed that an inventor of a patented technology is also an owner of that patent, as it is unusual that inventors give away their patents to drug companies without benefiting from them and without having any working relationship with that particular company. Noel Wathion has explained to us that Professor Rasi is not the owner of the patents for which he is named as inventor. We acknowledge Mr Wathion’s statement that Professor Rasi has never had, and does not have, any economic rights or financial interest or benefit (whether actual or potential) in, or arising from, any of the patents to which the Publication refers.

As concerns the employment of people, there are legal procedures to follow, but it is also common that the employer contacts people informally, encouraging them to apply for the post. However, the EMA has stated to us that Professor Rasi did not bring anyone to EMA from Sigma-Tau and that Stefano Marino was recruited according to the

Carter - Ruck Solicitors

6 St Andrew Street
London EC4A 3AE

T 020 7353 5005
F 020 7353 5553
DX 333 Chancery Lane
www.carter-ruck.com

Partners

Alasdair Pepper
Guy Martin
Nigel Tait
Ruth Collard
Cameron Doley
Claire Gill
Adam Tudor
Isabel Martorell

Partnership Secretary

Helen Burrluck

Authorised and regulated
by the Solicitors Regulation
Authority

SRA No. 44769

ordinary, rigorous EU selection procedures and received no favourable treatment at all.

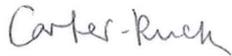
[And]

We apologize to Doctor Julie Williams and EMA for this mistake, which stems from the limited information that was available to us. In the material from the EMA that we had acquired, we could not see where this person worked and therefore looked her up on the Internet. Unfortunately, we found the wrong person, another Professor Julie Williams. Therefore, what we wrote about Julie Williams in our complaint to the EMA should be disregarded, apart from this sentence, which is correct:

"in Williams' 'Public declaration of interests' on the EMA's homepage from 21 November 2015 (13), no conflicts of interest are declared."

We look forward to hearing from you and hope this matter can now finally be resolved.

Yours faithfully



Carter-Ruck

26 September 2016

To Carter-Ruck solicitors

Referring to our letter from 11 September, you say that our position on identifying Guido Rasi and Stefano Marino in your email dated 23 August was actually very clear and beyond any possible misunderstanding. We believe we know best what our position is but apologize if we were not sufficiently clear about this.

We do not agree that we treat people differently, as we mention all three names in our apology.

You state: "In light of your reluctance to accept our client's assurances and explanations, we propose that they are instead, at the very least, acknowledged. We have therefore set out below a further amendment to what we believe is the final wording of the apology, which we trust should be uncontroversial." Your suggested amendment is the underlined sentence:

Noel Wathion has explained to us that Professor Rasi is not the owner of the patents for which he is named as inventor. We acknowledge Mr Wathion's statement that Professor Rasi has never had, and does not have any economic rights or financial interest or benefit (whether actual or potential) in, or arising from, any of the patents to which the Publication refers.

Firstly, your suggested amendment misses the context. Secondly, Wathion has never made any such statement to us; this statement was made by Rasi's lawyers, Carter-Ruck solicitors. Thirdly, the amendment is not necessary, as we had already previously acknowledged Wathion's explanations:

"We were not aware of the legal subtleties and assumed that an inventor of a patented technology is also an owner of that patent, as it is highly [you asked us to delete "highly", which we accepted to do] unusual that inventors give away their patents to drug companies without benefiting from them and without having any working relationship with that particular company. Noel Wathion has explained to us that Professor Rasi is not the owner of the patents for which he is named as inventor."

We accepted to take your suggested amendments into consideration, and we believe we have been very forthcoming in changing the text according to your wishes.

Sincerely,



Peter C Gøtzsche, DrMedSci, MSc
Director of the Nordic Cochrane Centre, Rigshospitalet
Professor, University of Copenhagen

Co-signatures:

Karsten Juhl Jørgensen, Deputy Director of the Nordic Cochrane Centre, Rigshospitalet
Tom Jefferson, Honorary Research Fellow, Centre for Evidence Based Medicine, Oxford, UK
Margrete Auken, MEP (The Greens/European Free Alliance)
Louise Brinth, PhD, MD, Danish Syncope Unit, Frederiksberg

Date: Fri, 30 Sep 2016 14:36:25 +0000
From: Helena Shipman <Helena.Shipman@carter-ruck.com>
To: "'Peter C. Gtzsche'" <pcg@cochrane.dk>
CC: "jefferson.tom@gmail.com" <jefferson.tom@gmail.com>,
"Margrete.Auken@ft.dk" <Margrete.Auken@ft.dk>,
"margrete.auken@europarl.europa.eu" <margrete.auken@europarl.europa.eu>,
"louisebrinth@live.dk" <louisebrinth@live.dk>, "kj@cochrane.dk"
<kj@cochrane.dk>, Debbie McLaren-Smith
<Debbie.McLaren-Smith@carter-ruck.com>, Adam Tudor
<Adam.Tudor@carter-ruck.com>
Subject: RE: Guido Rasi [CR-PCR1.FID114015]

Dear Sirs,

We refer to your email below.

Our client is prepared to accept your proposed wording of the apology, as it is imperative that the public is alerted as to the true state of matters, and in addition he has no desire to engage further in protracted correspondence and mutual inconvenience. For the avoidance of doubt, the agreed wording for the apology is as follows:

We apologize for our mistakes.

We were not aware of the legal subtleties and assumed that an inventor of a patented technology is also an owner of that patent, as it is unusual that inventors give away their patents to drug companies without benefiting from them and without having any working relationship with that particular company. Noel Wathion has explained to us that Professor Rasi is not the owner of the patents for which he is named as inventor.

As concerns the employment of people, there are legal procedures to follow, but it is also common that the employer contacts people informally, encouraging them to apply for the post. The EMA has stated to us that Professor Rasi did not bring anyone to EMA from Sigma-Tau and that Stefano Marino was recruited according to the ordinary, rigorous EU selection procedures and received no favourable treatment at all.

[And]

We apologize to Doctor Julie Williams and EMA for this mistake, which stems from the limited information that was available to us. In the material from the EMA that we had acquired, we could not see where this person worked and therefore looked her up on the Internet. Unfortunately, we found the wrong person, another Professor Julie Williams. Therefore, what we wrote about Julie Williams in our complaint to the EMA should be disregarded, apart from this sentence, which is correct:

in Williams Public declaration of interests on the EMAs homepage from 21 November 2015 (13), no conflicts of interest are declared.

Please confirm that the above apology will be published on the Nordic Cochrane website by no later than close of business on **Wednesday 5 October 2016**.

We look forward to hearing from you.

Yours faithfully,

Carter-Ruck

Helena Shipman
Solicitor, Carter-Ruck
helena.shipman@carter-ruck.com

Carter-Ruck Solicitors
6 St Andrew Street
London EC4A 3AE
T 020 7353 5005
F 020 7353 5553
DX 333 Chancery Lane
www.carter-ruck.com

One of the UK's best-known law firms, Carter-Ruck has a longstanding reputation for its expertise in the field of litigation and dispute resolution.

[Home](#) | [Media Law](#) | [International](#) | [Commercial Disputes](#) | [News](#)

Carter-Ruck is a CarbonNeutral® company. Think of the environment. Do you need to print this email?

From: "Peter C. Gøtzsche" [mailto:pcg@cochrane.dk]
Sent: 27 September 2016 12:13
To: Helena Shipman
Cc: jefferson.tom@gmail.com; Margrete.Auken@ft.dk; margrete.auken@europarl.europa.eu; lousebrinth@live.dk; kj@cochrane.dk; Debbie McLaren-Smith; Adam Tudor
Subject: Re: Guido Rasi

26 September 2016

To Carter-Ruck solicitors

Referring to our letter from 11 September, you say that our position on identifying Guido Rasi and Stefano Marino in your email dated 23 August was actually very clear and beyond any possible misunderstanding. We believe we know best what our position is but apologize if we were not sufficiently clear about this.

We do not agree that we treat people differently, as we mention all three names in our apology.

You state: In light of your reluctance to accept our client's assurances and explanations, we propose that they are instead, at the very least, acknowledged. We have therefore set out below a further amendment to what we believe is the final wording of the apology, which we trust should be uncontroversial. Your suggested amendment is the underlined sentence:

Noel Wathion has explained to us that Professor Rasi is not the owner of the patents for which he is named as inventor. We acknowledge Mr Wathion's statement that Professor Rasi has never had, and does not have any economic rights or financial interest or benefit (whether actual or potential) in, or arising from, any of the patents to which the Publication refers.

Firstly, your suggested amendment misses the context. Secondly, Wathion has never made any such

statement to us; this statement was made by Rasis lawyers, Carter-Ruck solicitors. Thirdly, the amendment is not necessary, as we had already previously acknowledged Wathions explanations:

We were not aware of the legal subtleties and assumed that an inventor of a patented technology is also an owner of that patent, as it is highly [you asked us to delete highly, which we accepted to do] unusual that inventors give away their patents to drug companies without benefiting from them and without having any working relationship with that particular company. Noel Wathion has explained to us that Professor Rasi is not the owner of the patents for which he is named as inventor.

We accepted to take your suggested amendments into consideration, and we believe we have been very forthcoming in changing the text according to your wishes.

Sincerely,

Peter C Gøtzsche, DrMedSci, MSc
Director of the Nordic Cochrane Centre, Rigshospitalet
Professor, University of Copenhagen

Co-signatures:

Karsten Juhl Jørgensen, Deputy Director of the Nordic Cochrane Centre, Rigshospitalet
Tom Jefferson, Honorary Research Fellow, Centre for Evidence Based Medicine, Oxford, UK
Margrete Auken, MEP (The Greens/European Free Alliance)
Louise Brinth, PhD, MD, Danish Syncope Unit, Frederiksberg

From: Helena Shipman <Helena.Shipman@carter-ruck.com>
To: "Peter C. Gøtzsche" <pcg@cochrane.dk>
CC: "jefferson.tom@gmail.com" <jefferson.tom@gmail.com>,
"Margrete.Auken@ft.dk" <Margrete.Auken@ft.dk>,
"margrete.auken@europarl.europa.eu" <margrete.auken@europarl.europa.eu>,
"louisebrinth@live.dk" <louisebrinth@live.dk>, "kj@cochrane.dk"
<kj@cochrane.dk>, Debbie McLaren-Smith
<Debbie.McLaren-Smith@carter-ruck.com>, Adam Tudor
<Adam.Tudor@carter-ruck.com>
Subject: RE: Guido Rasi [CR-PCR1.FID114015]
Date: Thu, 6 Oct 2016 17:08:22 +0000

Dear Sirs,

We refer to our email below.

Please confirm by return that you will publish forthwith the apology set out in our email, now agreed between the parties, and in any event by no later than close of business tomorrow, Friday 7 October.

We look forward to hearing from you.

Yours faithfully,
Carter-Ruck

Helena Shipman
Solicitor, Carter-Ruck
helena.shipman@carter-ruck.com

Carter-Ruck Solicitors
6 St Andrew Street
London EC4A 3AE
T 020 7353 5005
F 020 7353 5553
DX 333 Chancery Lane
www.carter-ruck.com

One of the UK's best-known law firms, Carter-Ruck has a longstanding reputation for its expertise in the field of litigation and dispute resolution.

[Home](#) | [Media Law](#) | [International](#) | [Commercial Disputes](#) | [News](#)

7 October 2016

Dear Helena Shipman,

We will upload our apology on the Nordic Cochrane Centre's website under <http://nordic.cochrane.org/research-highlights> on Monday 10 October.

yours sincerely

Peter C Gøtzsche, DrMedSci, MSc, Director and Professor, the Nordic Cochrane Centre
Karsten Juhl Jørgensen, MD, DrMedSci, Deputy Director, the Nordic Cochrane Centre
Tom Jefferson, MD, Honorary Research Fellow, Centre for Evidence Based Medicine, Oxford, UK
Margrete Auken, MEP (The Greens/European Free Alliance)
Louise Brinth, MD, PhD, Danish Syncope Unit, Frederiksberg

10 October 2016

Follow-up on our complaint to the European Medicines Agency (EMA) over maladministration at the EMA related to safety of the HPV vaccines

On May 2016, we submitted a [Complaint to the European Medicines Agency \(EMA\) over maladministration at the EMA](#) related to safety of the HPV vaccines.

The replies we received from the EMA came in three parts:

1. On 17 June, Noël Wathion, the EMA's Deputy Executive Director, addressed conflicts of interest issues related to the EMA's Executive Director, Guido Rasi ([2 pages](#)).
2. On 1 July, Noël Wathion sent the EMA's response to the other issues we had raised ([17 pages](#)).
3. Starting on 8 July and ending on 30 September, Carter-Ruck solicitors in London sent a total of 8 letters to us on behalf of their client, Guido Rasi, which we responded to.

The EMA's replies to us did not fully address our concerns. Some of our concerns were not addressed at all, and several of the EMA's statements were either wrong or seriously misleading, or irrelevant for the criticism we had posed. We have therefore today submitted a [Complaint to the EU ombudsman over maladministration at the EMA](#) related to safety of the HPV vaccines.

The EMA has made us aware that we have misinterpreted some of the information that was available to us in relation to conflicts of interest issues and we therefore make corrections here as well as in our [Complaint to the EU ombudsman over maladministration at the EMA](#) related to safety of the HPV vaccines. We have included the entire correspondence between Wathion and Rasi's law firm and us in an Appendix to our complaint to the ombudsman, as we believe it has considerable public interest.

About the EMAs executive director, we wrote in our complaint to the EMA:

"We noticed a Guido Rasi's name associated with patents for inventions and wonder whether this is the same person who is the EMA's director. If so, we believe Rasi has failed to declare his conflicts of interest."

"a Guido Rasi, which we assume is the same person, holds a number of patents, some of which were filed or approved in 2012 or 2013, and where the applicant was a drug company (Applicant: SciClone Pharmaceuticals, Inc.; Inventors: Guido Rasi, Enrico Garaci, Francesco Bistoni, Luigina Romani, Paolo Di Francesco) (15). As they go back less than five years, we believe he should have declared them, according to the EMA's regulations concerning the handling of declared interests of its employees (16)."

“the EMA’s director, Guido Rasi, has brought in a number of people from the drug company Sigma Tau that include Stefano Marino, his head of legal affairs. Rasi has worked with this company for many years and apparently owns several patents together with the company (15).”

“the EMA’s director, Guido Rasi, declared on 20 July 2015 that he had no conflicts of interest (14). On a form called ‘EMA Public Declaration of Interests,’ he replied ‘none’ to all four questions, also to question 4, which is: ‘Other interests or facts whether or not related to the pharmaceutical industry⁴ which you consider should be made known to the Agency and the public, including matter relating to members of your household⁵.’”

The EMA’s deputy executive director, Noël Wathion, has informed us that:

“EMA staff members are required to declare in their declaration of interests (DoI) any ownership of a patent held for a period of 5 years prior to the start of employment with the Agency.”

“the inventor mentioned on a patent is the creator of the invention and is always entitled to be designated on the patent, regardless of who files the patent application or owns the patent. An inventor remains an inventor throughout the term of a patent, but he is not necessarily the owner of the patent, e.g. the ownership rights may be vested originally upon, or subsequently assigned to, a subject other than the inventor/s. Only the owner of a patent can enjoy economic rights with regard to that particular invention. Therefore, neither the applicable rules, nor considerations of common sense oblige EMA staff to declare in their DoI any patents for which they are the inventor/s, but not the owner/s, unless the inventor is entitled to financial benefits (e.g. lump-sum or royalties) stemming from the exploitation of the invention.”

“The Agency’s Executive Director Prof Rasi is indeed mentioned on a number of patents, even beyond those referred to in footnote 15 of your complaint letter, but only as inventor, not as owner of the patents. Prof Rasi does not own any patent together with Sigma-Tau. He is named as inventor on 2 patent families for which Sigma-Tau is named as applicant or patentee. He is not even the beneficiary of those patent families. Hence there was and there is no obligation for him to declare these patents in his DoI as EMA staff member in accordance with EMA’s proceedings on the handling of DoIs.”

“We would also like to clarify that Prof Rasi has never worked with or for Sigma-Tau and that no former Sigma-Tau employee joined EMA since 2011 with the exception of Mr S. Marino, who was indeed the former General Counsel at Sigma-Tau, as publicly announced by EMA when he was hired after a very rigorous competition run by a selection panel featuring also external members from the Legal Service of the European Commission. Prof Rasi was not part of that selection panel and he did not know Mr Marino when he was still working in industry. The statements appearing at page 17 of the Nordic Cochrane complaint against EMA have therefore no foundation.”

We apologize for our mistakes.

We were not aware of the legal subtleties and assumed that an inventor of a patented technology is also an owner of that patent, as it is unusual that inventors give away their patents to drug companies without benefiting from them and without having any working relationship with that

particular company. Noel Wathion has explained to us that Professor Rasi is not the owner of the patents for which he is named as inventor.

As concerns the employment of people, there are legal procedures to follow, but it is also common that the employer contacts people informally, encouraging them to apply for the post. The EMA has stated to us that Professor Rasi did not bring anyone to EMA from Sigma-Tau and that Stefano Marino was recruited according to the ordinary, rigorous EU selection procedures and received no favourable treatment at all.

About the EMA's rapporteur, we wrote:

"We also believe that the rapporteur for the EMA's report, Julie Williams (2), has failed to declare her conflicts of interest."

We apologize for this mistake, which stems from the limited information that was available to us. In the material from the EMA that we had acquired, we could not see where this person worked and therefore looked her up on the Internet. Unfortunately, we found the wrong person, another Professor Julie Williams. Therefore, what we wrote about Julie Williams in our complaint to the EMA should be disregarded, apart from this sentence, which is correct:

"in Williams' 'Public declaration of interests' on the EMA's homepage from 21 November 2015 (13), no conflicts of interest are declared."

Sincerely,



Peter C Gøtzsche, Professor, Director of the Nordic Cochrane Centre, Rigshospitalet, Denmark
Karsten Juhl Jørgensen, Deputy Director of the Nordic Cochrane Centre, Rigshospitalet, Denmark
Tom Jefferson, Honorary Research Fellow, Centre for Evidence Based Medicine, Oxford, UK
Margrete Auken, MEP (The Greens/European Free Alliance)
Louise Brinth, PhD, MD, Danish Syncope Unit, Frederiksberg, Denmark