



## European Ombudsman

**Emily O'Reilly**  
European Ombudsman

Prof. Guido Rasi  
Executive Director  
European Medicines Agency  
30 Churchill Place  
Canary Wharf  
London E14 5EU  
ROYAUME-UNI

Strasbourg, 27/10/2014

Complaint OI/3/2014/(BEH)FOR

Dear Professor Rasi,

Thank you for assisting my services in relation to the present inquiry. My services have carefully examined the redacted versions of CSR M02-404, CSR M04-691 and CSR M05-769, the non-redacted versions and the internal and external correspondence of EMA relating to the redactions.

I note that the letter dated 11 April 2014 to the person seeking public access to CSR M02-404, CSR M04-691 and CSR M05-769 provides a brief description of what has been redacted from the requested documents. However, the letter does not specify, in any detail, why that information has been redacted.

It is obvious, from a close reading of the documents, that certain redactions may be justified to protect the personal data of patients (for example, the redacted text from pages 258 to 314 of CSR M02-404, the redacted text from pages 142 to 147 of CSR M04-691 and pages 305 to 381 of CSR M05-769). Certain other redactions, which mention the names of companies that provided services to AbbVie, or the names of software used by AbbVie, are not, in my view, problematic, as they may be considered to relate to the confidential business relationships of AbbVie.

However, I have doubts and concerns as regards other redactions. In this context, I request EMA to answer the following questions.

1) The released sections of CSR M02-404, CSR M04-691 and CSR M05-769, describe the selection and timing of doses of adalimumab for each subject (section 9.4.5). However, the rationale for choosing the doses for the study has been partially redacted in all three CSRs (Sections 9.4.4). No specific justification for this redaction has been put forward in the letter to the person seeking public access.

It might be understood, from the letter of 11 April 2014, that EMA is of the view



that the information redacted from all three CSRs has "relevance to an on-going development".

The Ombudsman first requests EMA to confirm (**Question 1(a)**) if AbbVie has informed EMA what this on-going development is. Or, alternatively, has EMA relied on the unsubstantiated assertion of AbbVie that the redacted information relates to an "on-going development".

A review of the non-redacted documents reveals that while the redacted text does contain a reference, in very general terms, to a "development programme", it does not contain any description of that development programme. It is thus difficult to understand why releasing this data would reveal any information about an on-going development programme and thus, why releasing this data would undermine a legitimate interest of AbbVie.

The Ombudsman also notes that the CSRs in question date from 2006 and 2009. Can EMA confirm (**Question 1(b)**) whether the development programme referred to in Sections 9.4.4. is in the public domain now.

Can EMA explain (**Question 1(c)**) why it considers it justified to redact information concerning the rationale for dosage selection from Section 9.4.4 when much of the substantive information redacted from that section is disclosed in Section 9.4.5?

If EMA is of the view that the redacted information would enhance the ability of competitors to design their own testing programmes, the Ombudsman requests EMA to confirm (**Question 1(d)**) if the redacted text refers to any novel aspect of the process of selection of doses.

2) EMA has redacted considerations used in determination of sample size from all three CSRs. The Ombudsman first notes that the determination of sample size would appear to be a vital element to a CSR.

As regards CSR M02-404, please explain in detail (**Question 2(a)**) the reasons for redacting the sentence from Section 9.7.1.2 (page 133). There does not appear to be any evident justification for the redaction of this sentence.

As regards CSR M02-404, please explain in detail (**Question 2(b)**) the reasons for redacting the second sentence from Section 9.7.2 (page 138). As regards this question, the Ombudsman notes that the internal communications of the EMA staff who reviewed the suggested redactions of AbbVie do not identify this information in Section 9.7.2 as commercially confidential (see internal email entitled Humira docs of 11 March 2014 at 14:08). Rather, the internal communications of the EMA staff suggest that the redacted information reflects standard practice in clinical trials. The Ombudsman notes that, eventually, the view was taken (see internal email entitled "Humira docs" of 28 March 2014 at 14:20) that the redaction was acceptable because the redaction "does not harm the understanding of the CSR". The Ombudsman reminds EMA that a redaction can only be justified if the release of the information would undermine a legitimate interest set out in Article 4 of Regulation 1049/2001. The argument that a redaction does not harm the understanding of a document is irrelevant as regards the application of Regulation 1049/2001.

3) EMA has redacted the entire sections describing protocol and statistical changes from each CSR (sections 9.8.1 and 9.8.2).



On 8 April 2014, EMA provided the Ombudsman with the redacted documents and a very brief explanation for the agreed redactions. The explanation stated, as regards all three CSRs that:

"Protocol and statistical changes: The section on protocol and statistical analysis changes has been deleted to avoid misinterpretation as the initial protocol and statistical analysis plan are not part of the body of this CSR, which is being released."

The Ombudsman first notes that while this text was redacted from the released documents, no reference is made to these redactions in the letter to the complainant of 11 April 2014. Can EMA explain (**Question 3(a)**) why EMA failed to inform the person seeking access that it was redacting this information?

As regards the redaction of protocol changes, the Ombudsman has carefully reviewed the redacted text. She finds no obvious reason why the release of the redacted text relating to protocol changes (section 9.8.1) would undermine a legitimate commercial interest of AbbVie.

The Ombudsman view would seem to be supported by the internal email of EMA staff (see internal email entitled "Humira docs" of 11 March 2014 at 14:08).

The Ombudsman thus requests EMA (**Question 3(b)**) to provide her with a detailed justification for the redactions, explaining clearly why the release of the redacted text in Section 9.8.1 would undermine a legitimate commercial interest of AbbVie.

Further, the Ombudsman is aware that many clinical studies will involve protocol changes. She is also aware that it is important, for the validity of such studies and the conclusions drawn from them, that such protocol changes be described and justified. In light of this observation, can EMA take a view (**Question 3(c)**) as regards whether there is always an overriding public interest in the disclosure of the information on protocol changes?

As regards the redaction of Section 9.8.2 from all three CSRs, namely the section on "Changes from the Protocol to the statistical analysis plan", please explain in detail (**Question 3(d)**) why any specific information in Section 9.8.2 relating to statistical methods remains novel today. In this respect, please explain in detail (**Question 3(e)**) why EMA did not take due account of the view taken by the EMA expert in an internal email (see internal email entitled "Humira docs" of 11 March 2014 at 14:08), namely, that the testing methods redacted are "commonly used in statistics" today and would nowadays be mentioned in an EPAR (the expert seems to agree that the methods may have been novel when the CSR was first drafted).

Further, the Ombudsman is aware that it is important, for the validity of such studies and the conclusions drawn from them, that such changes to a statistical plan be described and justified. In light of this observation, can EMA take a view (**Question 3(f)**) as regards whether there is always an overriding public interest in the disclosure of the information on statistical plans used and the changes thereto?

4) As regards all three CSRs, EMA has redacted the text from section 11.4.2.4 (multi-centre studies). There is no explanation, in the letter granting partial access, for this redaction. The Ombudsman has carefully reviewed the redacted



text. She finds no obvious reason why the release of the redacted text would undermine a legitimate commercial interest of AbbVie. The Ombudsman requests EMA to provide her with a detailed justification (**Question 4**) for the redaction, explaining clearly why the release of the redacted text would undermine a legitimate commercial interest of AbbVie.

5) As regards CSR M02-404, the email entitled "Humira docs" of 11 March 2014 at 14:08 refers, in Point V, to the proposed redaction of statistical methods. Can EMA confirm expressly (**Question 5**) that no information relating to statistical methods was redacted from the public version of CSR M02-404?

6) As regards CSR M04-691, please provide a justification (**Question 6**) for the redactions from pages 25-28 and page 40).

7) As regards CSR M04-691, EMA has redacted a detailed description of assay for drug concentration measurements (Section 9.5.4). EMA links this information to an immunogenicity assay. Can EMA explain (**Question 7(a)**) this link to the Ombudsman?

Please explain in detail (**Question 7(b)**) why the process described is novel. Is all of the redacted information novel (**Question 7(c)**)? Given that the CSR dates from 2006, is the process described still novel today (**Question 7(d)**)?

Would the redacted information be necessary or even useful to allow an informed third party to evaluate the reliability and meaning of the CSR (**Question 7(e)**)?

8) As regards CSR M04-691, EMA states that it has redacted what it refers to as "exploratory subgroups analysis" linked to "sub-indications" and an "on-going development".

The Ombudsman understands that this redaction principle refers to the redactions made to Section 11.4.1.3.2 (Subgroup Analyses of Clinical Response at Week 4) on pages 127-130.

First, certain redactions do not appear to relate to sub-indications or any on-going development, but rather refer to the analysis of, as the title of the section suggests, the impact of Humira on certain defined subgroups of patients. Can EMA explain how each redaction relates to sub-indications (**Question 8(a)**)?

If any sub-indication is revealed by such the redacted information, can EMA indicate to the Ombudsman (**Question 8(b)**) the precise lines of the redacted text which contains that information? If any sub-indication is identified, can EMA expressly confirm (**Question 8(c)**) if a marketing authorisation has been sought for that indication since the CSR was submitted in 2006. If any sub-indication is identified, can EMA expressly confirm (**Question 8(d)**) whether Humira is currently prescribed off-label for that sub-indication?

Can EMA please indicate to the Ombudsman (**Question 8(e)**) the precise lines from the redacted text which relate to an on-going development? The Ombudsman also notes that the CSR dates to 2006. Is the development referred to still, 8 years later, an on-going development (**Question 8(f)**)?

The Ombudsman notes that some of the redacted text from the list on the top of page 127 is contained in non-redacted text later in the CSR. Can EMA explain, in this context, why the text on the top of page 127 is redacted (**Question 8(g)**)?



The Ombudsman sees no obvious reason for redacting the sentence beginning on page 127 and continuing on to page 128. Can EMA explain the rationale for this redaction (**Question 8(h)**)?

Table 28 has been redacted. It does not appear to relate to sub-indications or on-going developments, but rather the standard effects of Humira. Please explain in detail why table 28 has been redacted (**Question 8(i)**).

The text redacted at the bottom of page 129 would appear to have important clinical value. Can EMA explain why this text is redacted as it does not obviously relate to an on-going development or an unexploited sub-indication (**Question 8(j)**). Please take a detailed position as regards whether there is a public interest in the disclosure of this information which would override any interest in non-disclosure (**Question 8(k)**).

Table 29 has been redacted. It does not appear to relate to sub-indications or on-going developments, but rather the standard effects of Humira. Please explain in detail why table 29 has been redacted (**Question 8(l)**).

The correspondence between AbbVie and EMA examined by the Ombudsman (see email of 25 March 2014 at 13.55) refers to AbbVie's current development of Humira (see last main paragraph of that email). An example is given relating to exploratory analyses in CSR M04-691. Can EMA expressly confirm if the developments referred to are currently of relevance to the clinical use of Humira, either on-label or off label (**Question 8(m)**)? In relation to this question, please confirm if researcher/practitioners could use this information to understand better the overall risk-benefit of Humira to treat patients, either on-label or off label?

9) As regards CSR M04-691, EMA has redacted the sentence contained in Section 11.4.2.4 (Multi-centre studies). No justification has been put forward for this redaction and no justification appears obvious to the Ombudsman. Can EMA justify this redaction (**Question 9**)?

10) As regards CSR M05-769, EMA has redacted text from page 10-13 (Efficacy Results) and page 16 (Conclusions).

The Ombudsman has serious concerns relating to the redactions on page 10 (identical text is redacted from section 11.4.1.3.1 on secondary variables-mucosal ulcerations (page 231) and section 11.4.7 on Efficacy Conclusions (page 277). These redactions appear to remove important clinical information. Moreover, the text that has been left in is, as a result of the redaction, potentially misleading.

As regards the redaction from the 4th bullet point on page 10: please justify, specifically, the redaction of the first word (**Question 10(a)**); please justify, specifically, the redaction of the 9th and 10th words (**Question 10(b)**); and please justify, specifically, the redactions from the remainder of the sentence (**Question 10(c)**). Can EMA confirm that the redactions from the 4th bullet point on page 10 alter, somewhat, the meaning of the text (**Question 10(d)**). Can EMA comment on the importance, in terms of understanding the efficacy of Humira, of the fourth bullet point on page 10 (**Question 10(e)**)?

As regards the redaction from the 5th bullet point on page 10, please justify, specifically, why this entire bullet point has been redacted (**Question 10(f)**).



Can EMA comment on the importance, in terms of understanding the efficacy of Humira, of the 5th bullet point on page 10 (**Question 10(g)**)?

As regards the redaction from the 6th bullet point on page 10, please justify why this bullet point has been redacted (**Question 10(h)**). Can EMA comment on the importance, in terms of understanding the efficacy of Humira, of the 6th bullet point on page 10 (**Question 10(i)**)? Can EMA confirm that the redactions from the 4th bullet point on page 10 can lead to a misunderstanding of the text (**Question 10(j)**)?

As regards the redaction on page 11 (the last sentence of the first bullet point of the sub-section entitled "Results of patient-reported outcomes"), please justify, specifically, the redaction (**Question 10(k)**). Can EMA confirm that the redaction alters, somewhat, the meaning of the bullet point (**Question 10(l)**). The redaction would appear to have certain clinical value (even if, as a patient reported outcome, it may not be decisive as regards the granting of the marketing authorisation sought). Can EMA comment on the importance for clinicians and patients, in terms of understanding the overall impact and efficacy of Humira, of the redaction on page 11 (**Question 10(m)**)? As regards this redaction, the Ombudsman notes the internal email of EMA (28 March 2014 at 14.20) where the existence of a rationale for this redaction is questioned. The Ombudsman recalls that every redaction must be justified on the basis of an exception set out in Regulation 1049/2001. What is the rationale, under Regulation 1049/2001, for this specific redaction (**Question 10(n)**)?

As regards the redaction on pages 12 and 13 (the 7 bullet points of the sub-section entitled "Results of histology and histochemistry parameters"), please justify, specifically, the redactions (**Question 10(o)**). Can EMA comment on the importance, in terms of understanding the overall efficacy of Humira, for both on-label and off-label use, of the redaction on page 11 (**Question 10(p)**).

EMA has redacted related text from Section 9.5.1.1.6 (Histology) and Section 9.5.1.1.7 (Histochemistry). The redactions seem to refer to testing methods and or testing design. Can EMA explain in what manner these testing methods or testing designs remain novel in 2014, taking into account the fact that the CSR dates from 2009 (**Question 10(q)**)? Without prejudice to the need to justify why the release of the data would undermine an interest set out in Article 4 of Regulation 1049/2001, does EMA consider that the redacted text should be disclosed in the public interest (**Question 10(r)**)?

EMA has redacted the related tables on pages 254 and 255, which set out the results of these tests? Please also, in this context, explain and justify (**Question 10(s)**) the redactions from the text on pages 255-261 (histology) and 262-268 (histochemistry). In this context, the Ombudsman notes that similar redaction are carried out from page 280 and 281 in the section on Efficacy Conclusions.

As regards the redactions on page 16 (and the identical redactions on page 389), the Ombudsman has failed to identify any possible legitimate commercial interest that might be affected by the disclosure of this text. Please explain and justify, specifically, the redactions (**Question 10(t)**).

The redactions on page 16 (and the identical redactions on page 389) appear to alter the meaning of the text. Can EMA comment on the importance, in terms of understanding the efficacy of Humira, of the redactions (**Question 10(u)**)? In this context, the Ombudsman notes that the redactions have been made to sections which are described as "Conclusions" and "Overall Conclusions" of the



CSR. Without prejudice to the need to justify why the release of the data would undermine an interest set out in Article 4 of Regulation 1049/2001, does EMA consider that the redacted text should be disclosed in the public interest (**Question 10(v)**)?

**11)** As regards CSR M05-769, EMA has redacted text a bullet point on page 174, two bullet points on page 175, 5 bullet points on page 176 and 3 bullet points on page 177 (secondary endpoints).

Please comment, as regards each specific redacted bullet point, on whether the information redacted from CSR M05-769 relating to secondary endpoints may relate to the broad understanding of the risk-benefit of Humira as regards the indication for which the marketing authorisation was sought and/or for other indications (**Question 11(a)**). As regards such other indications, please indicate whether, currently, such other indications are treated off-label with Humira (**Question 11(b)**). If so, does the redacted information allow for at least a better understanding of the risk-benefit of Humira for treating (off-label) such indications (**Question 11(c)**)?

The correspondence between AbbVie and EMA examined by the Ombudsman (see email of 25 March 2014 at 13.55) refers to "AbbVie's current development of Humira" (see last paragraph of page 2 of the email). Examples are given. Can EMA expressly confirm if these developments are currently of relevance to the clinical use of Humira, either on-label or off label (**Question 11(d)**)?

Please explain why, given that such information on secondary endpoints may relate to the overall efficacy of the tested product (both in relation to its use to treat Crohn's disease or other indications), whether there is an overriding public interest in the disclosure of such information (**Question 11(e)**).

**12)** As regards CSR M05-769, EMA has redacted text from page 235. These redactions would appear to have some clinical value. Moreover, the text that has been left is, as a result of the redaction, potentially misleading.

Please explain and justify the redactions from the following sentence beginning "Subjects in the adalimumab group demonstrated a (redacted) greater (redacted) change in CDEIS score from Baseline" (**Question 12(a)**).

As regards the other redactions on page 235, the Ombudsman notes that what is being tested in this section is not redacted (namely, a change in CDEIS score from Base line to Week 12 and Week 52 compared subjects in the placebo group). However, the results of these tests are redacted. Can EMA explain and justify these redactions (**Question 12(b)**)?

**13)** As regards CSR M05-769, EMA has redacted text from page 236 (Section 11.4.1.3.3). These redactions would appear to have some clinical value.

The Ombudsman notes that what is being tested is not redacted (simple endoscopic score for Crohn's disease (SES-CD) Endpoints). However, the manner in which these tests are carried out and the results of these tests are redacted. Can EMA explain and justify these redactions (**Question 13**)?

**14)** As regards CSR M05-769, EMA has redacted text from page 245 (Section 11.4.1.4.1). These redactions would appear to have certain clinical value (even if they may not be decisive as regards the granting of the marketing authorisation sought).



As regards this redaction, the Ombudsman notes the statement in the internal email of EMA (28 March 2014 at 14.20) where the existence of a rationale for this redaction is questioned. The Ombudsman recalls that every redaction must be justified on the basis of an exception set out in Regulation 1049/2001. EMA is requested to explain the rationale for this specific redaction (**Question 14**)?

**15)** As regards CSR M05-769, EMA has redacted text from Section 13.1 (Discussion and Overall Conclusions).

The redactions in the paragraph commencing on page 385 and ending on page 386 (in the sub-section marked Discussion) appears, at first sight, to have important research and clinical implications. There does not appear to be any obvious justification for these redactions. Can EMA explain and justify these redactions (**Question 15(a)**).

The redaction of text from the second full paragraph on page 386 would appear to alter the meaning of the text. Can EMA explain and justify the redaction (**Question 15(b)**)?

Can EMA explain and justify the redaction on page 387 (**Question 15(c)**)?

The letter of EMA to the complainant refers to "exploratory secondary endpoints results and theories linked to on-going development". Has AbbVie informed EMA of what this on-going development is or has AbbVie simply made the assertion that the data relates to an on-going development without describing to EMA what this "on-going development" is (**Question 15(d)**)?

Please confirm and explain, bullet point by bullet point, which specific information on pages 174 to 177 relates to an "on-going development" (**Question 15(e)**).

As regards the redaction from the bullet on page 174: please justify, specifically, the redaction of the first word (**Question 15(f)**); and please justify, specifically, the redaction of the 6th and 7th words (**Question 15(g)**). Does EMA agree that the redaction of the first word alters the meaning of the text (**Question 15(h)**)? As regards the 6th and 7th words, does the redacted information refer to a now well-known procedure in relation to evaluating Crohn's disease (**Question 15(i)**)?

As regards the redaction from the 2 related bullet points on page 175, please justify, specifically, the redactions, and in particular explain why the redacted bullet points should be treated differently from the previous bullet points, which are not redacted (**Question 15(j)**).

**16)** EMA has redacted "Lot number Information" from CSR M02-404, CSR M04-691 and CSR M05-769. No justification for this redaction has been put forward in the letter to the person seeking public access. Further, the Ombudsman has not seen, amongst the inspected documents, any explanation as regards why the release of Lot number Information might damage any legitimate commercial interests of Abbvie. Can EMA explain in what manner the release of lot numbers would undermine a legitimate commercial interest of AbbVie (**Question 16**)?



Please note that the reference number of this case has been changed to OI/3/2014/(BEH)FOR. I would be grateful if your reply could reach me by 31 January 2015.

Please note that the substantive information contained in the above questions is taken from the versions of the CSRs which have been made public by EMA. As such, I take the view that I can make public the present letter. If you have any comments in relation to my intention to make public the present letter, you should provide me with such comments within 10 working days of the receipt of the present letter.

Yours sincerely,

Emily O'Reilly