European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

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OVERVIEW OF COMMENTS RECEIVED ON THE REFLECTION PAPER ON PUBLICATION OF CHMP NEGATIVE OPINION AND REFUSAL OF MARKETING AUTHORISATION APPLICATIONS FOR HUMAN MEDICINAL PRODUCTS

Table 1: Organisations that commented on the Guideline as released for consultation

Add name followed by link to individual received comment (upon publication by Web Services)

	Name of Organisation or individual	Country
1	EFPIA	Belgium
2	Novo Nordisk	Denmark
3	PhRMA	Belgium
4	F. Hoffmann – La Roche	Switzerland

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Table 2:Discussion of comments

GENERAL COMMENTS - OVERVIEW	Outcome
[EFPIA] It is necessary to ensure that information on negative CHMP opinions is managed in such a way it does not compromise a possible future for the product if a re-examination is requested or a new application is filed at a later date. In contrast with Article 11 of the Regulation, on publication of withdrawals, there is no provision in Article 12(3) requiring publication of an assessment report in case of a refusal. In case of refusal of authorisation for new medicinal products, the information requested by the legislator in Article 12 (3) of Regulation EC 726/2004 will be provided in the Q&A document.	Those general comment are addressed below under the section on "Specific comments on text", in particular the subsection 3 related to the structure an content of the documents to be published. In addition, this reflection paper on publication on negative opinion and refusal should be read in conjunction with the EMEA Principles to be applied for the Deletion of Commercially Confidential Information for the Disclosure of EMEA Documents (EMEA/45422/2006).
[PhRMA] PhRMA supports the EMEA initiatives to increase transparency vis-à-vis stakeholders, in particular patients and healthcare professionals. However, an appropriate balance should be struck between the various interests. Like for the other transparency measures, there is a clear need to preserve confidentiality of commercial information. Protection of confidential information is important at all stages of the application process because almost all information and documents provided by the applicant are confidential. The regulatory review process for medicines is based on the submission and assessment of very detailed and comprehensive technical and scientific data that result from time consuming and costly development programs, and the need to protect confidential information is more acute here than in most, if not all, other industry sectors. Protection of confidential information is also the natural counterpart of transparency. In addition, the reflection document does not propose a procedure in case the EMEA and the applicant disagree on the commercially confidential nature of a piece of information. PhRMA's comments focus on the following aspects: • Definition of what constitutes commercially confidential information. • Some considerations on the applicant's involvement. • Establishment of a specific procedure to mitigate situations where the EMEA and an applicant disagree on the commercial confidentiality of a piece of information. Very often, a negative opinion is not based on a final negative conclusion, but rather on insufficient positive data or the inconclusive nature of the entire data package. It is important to remind the public that the conclusion may be different when new data become available.	

SPECIFIC COMMENTS ON TEXT		
2. LEGAL BASIS AND SCOPE		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
[Novo Nordisk] Page 2, 3rd paragraph	According to……for initial applications and also for certain post-authorisation application (e.g. variations related to extension of new therapeutic indications). A…… We suggest to change the sentence just before and in the brackets either: * delete "certain" before post-authorisation and delete "e.g." in brackets or * change the sentence in brackets to: "(type II variation for new indication and extension of marketing authorisation as set out in Annex II to Regulation (EC) No. 1085/2003))". We assume these cases are what is covered, so why not specify these to avoid confusions?	The section has been simplified to avoid any misunderstandings.

3. DOCUMENTS TO BE MADE AVAILABLE TO THE PUBLIC – TIMETABLES		
Line no.[2] + paragraph no.	**Comment and Rationale**	**Outcome**
[EFPIA] Paragraph 2 Sentence 1 Bullet 1 p. 3/6	The initial CHMP negative opinion will be made publicly available almost immediately. However, if the applicant/MAH requests a re-examination, such information will not be made publicly available until the next CHMP monthly report, i.e. between approximately 2 and 4 weeks after such a request is made, which seems unreasonable and is inconsistent with the EMEA Guideline on procedures for re-examination of CHMP opinions (EMEA/CHMP/50745/2005). The latter guideline states, in section 7, that at the time the EMEA receives written notice requesting a	Accepted

[1] Where applicable
[2] Where applicable

	re-examination, it will make this information public. Modify sentence as follows, for consistency with EMEA/CHMP/50745/2005: "*In case of request for re-examination of the opinion*, the Applicant's request will be announced ~~in the subsequent CHMP monthly report~~ **at the time the Agency receives written notice from the applicant/MAH requesting a re-examination**."	
Paragraph 2 p. 3/6	We very welcome the fact that the 'Q&A document, published at the time of the initial opinion, will be immediately removed and replaced by a Summary of Opinion'. It is necessary, to avoid confusion, that the EMEA does it immediately in case of request for re-examination of the opinion and a change in the final opinion (negative to positive). There should not be any ambiguity as to the current opinion of the CHMP at the time the public consult the website. For instance a person searching the web to look for information on rivastigmine (Prometax) may believe that the negative opinion given in 2005 is still current (**in the list** of opinions currently on the EMEA website there is no mention next to 2005 negative opinion to indicate a positive pinion given in 2006 supersedes the 2005 negative opinion.). The website should be maintained in such a way the public cannot be lead to believe that obsolete information may be current.	It is proposed that the Q&A is updated at the time of the re-examination opinion. Regarding some archiving issues related to past information, the issue is being investigated and will be addressed in due time.
Bullet 2 p. 3/6	The EMEA proposed to publish a Refusal EPAR following adoption of the Commission Decision. **In contrast with Article 11 of the regulation, on publication of withdrawals, there is no provision in Article 12(3) requiring publication of an assessment report in case of a refusal**. In addition, the publication of a EPAR when an MAA is refused appears to be inconsistent with the EMEA's practice of removing EPARs of authorised products from their website when those authorisations are withdrawn by the MAH. The EMEA should be consistent in its approach to the availability of information on products that will not be available to patients. While an EPAR update can be considered in case of refusal of post authorisation applications concerning authorised medicinal	Article 12(3) and 37(7) do not provide explicitly that it is the assessment reports that should be made publicly accessible. However, as an assessment report will exist from the assessment of the medicinal product and as the commercial sensitive information will be removed, this document provides for a practical basis for the publication. The assessment report is published for positive opinion and withdrawal of application, therefore publication of assessment report for refusal will also ensure consistency by providing the same level of information on all marketing authorisation applications to the public. Information on withdrawn marketing authorisation is a different issue.

	products**, there is no rationale for preparing and publishing a refusal EPAR** for new medicinal products, as refusal prohibits the placing on the market of the product in the EU. In the latter case, **the information requested by the legislator in Article 12 (3) of Regulation EC 726/2004 will be provided in the Q&A document,** the content of which is outlined in the annex to the draft Reflection paper.	
[PhRMA] 1st bullet point	It is not appropriate to publish the negative opinion of the CHMP in the event that the applicant has a filed a request for re-examination of that opinion If the decision of the CHMP becomes positive following the requested re-examination, the interests of the MA holder would be prejudiced by the initial publication of the negative opinion of the CHMP. This principle is already expressed in guidance for orphan medicines designation (EMEA/4795/00). *Amend the first bullet point as follows:* The negative opinion will be announced in the CHMP meeting Press Release of the CHMP meeting <u>following the meeting</u> during which the opinion is adopted <u>(where there is no request of re-examination) or during which the final opinion is adopted (after re-examination)</u>. A Question and Answer Document will be attached. (See template annexed). This Q&A document will replace existing Summary of opinion "Smop" for negative opinion. ~~*In case of request for re-examination of the opinion*, the Applicant's request will be announced in the subsequent CHMP monthly report. If the re-examination confirms the refusal, the Q&A document, published at the time of the initial opinion, will be immediately updated to reflect the outcome of the appeal. If the re-examination is followed by a positive opinion for marketing authorisation, the Q&A document, published at the time of the initial opinion, will be immediately removed and replaced by a Summary of Opinion.~~	Following the transparency measures adopted by the EMEA Management Board in 2001, the EMEA has published summaries of opinion (for both positive and negative opinion), as an attachment to the CHMP press-releases, since 1st April 2001.
1st bullet point, new sentence	The CHMP meeting Press Release and the Q&A document should not contain commercially confidential information. It is as much important for the Q&A document as for the Refusal EPAR. Because of the sensitive nature of the information contained in	It is now clearly stated in the document that the EMEA Principles for the deletion of commercially confidential information will apply to documents referred in the reflection paper.

	applications for marketing authorisation, applicants should be closely involved in preparing documents (e.g. CHMP meeting Press Release, Q&A, Refusal EPAR) for publication. Any undue publication of "commercially confidential information" could be detrimental to the applicant company; once a document containing commercially confidential information is published, the damage cannot be undone. *Add the following at the end of the first bullet point:* The CHMP meeting Press Release and the Q&A document will not contain any commercially confidential information.	
new paragraph	PhRMA considers it essential to clarify what is meant by "commercially confidential information." The term can adequately be defined by reference to the EMEA guidelines on principles to be applied for the deletion of commercially confidential information for the disclosure of EMEA documents. *Add the following at the end of the section:* For purposes of this document, the term "commercially confidential information" refers to the definition of "commercially confidential information" contained in the guidelines on principles to be applied for the deletion of commercially confidential information for the disclosure of EMEA documents.	It is now clearly stated in the document that EMEA Principles for the deletion of commercially confidential information will apply to document referred in the reflection paper.

4. STRUCTURE AND CONTENT OF THE DOCUMENTS TO BE PUBLISHED		
Line no[3]. + paragraph no.	**Comment and Rationale**	**Outcome**
[EFPIA] p. 3/6 "Question and Answer" document	The consequences of a negative opinion on development of the product are for the applicant to evaluate and should not be commented upon with the Q&A. In addition, a compassionate use programme may not always be operating. Suggest the following amendments.	Comment taken into account in revising this sentence.

[3] Where available

	This document ~~would~~ **will** highlight the main findings/concerns identified by the CHMP as well as potential consequences in terms of ~~development of the product~~, compassionate use programme **(if applicable)** and use of the product when it is already on the market.	
Paragraph 2 p. 3/6 "Question and Answer" document	The fact that the Company will be provided the Q&A to comment on it prior to its publication is appreciated. It would be helpful to indicate an approximate timeframe for this review, as it will probably be very short.	Timeframe added.
p. 3/6 Refusal EPAR	As indicated above, there is no rationale for preparing and publishing a refusal EPAR for new medicinal products and the information requested by the legislator in Article 12 (3) of Regulation EC 726/2004 will be provided in the Q&A document. The section on refusal EPAR should be amended accordingly.	See previous comment
Paragraph 2, 1st sentence p. 3/6	The wording of the statement regarding confidentiality considerations in relation to the 'CHMP views on the application' does not seem to be the most appropriate. It would seems more appropriate to state that 'the opinion of the CHMP on the application for marketing authorisations and the reasons for that opinion are not considered as confidential information.' The ~~*CHMP views*~~ ***opinion of the CHMP*** on an application ***for marketing authorisations and the reasons for that opinion*** cannot be considered as 'commercially confidential information', ……	Proposed wording revised
[Novo Nordisk] Page 3/6	Structure and content of the document to be published - Refusal EPAR line 9 from below: However it should be noted that it is the EMEA responsibility **add "in collaboration with the applicant"** whether or not to introduce the comments with regard to confidentiality.	Wording clarified in line with the reflection paper on withdrawal of marketing authorisation applications.
[PhRMA] 1st paragraph, 2nd sentence	The consequences of a negative opinion on development of the product are for the applicant to evaluate and should not be commented upon with the Q&A. In addition, a compassionate use programme may not always be operating.	Comment taken into account in revising this sentence.

	Amend the second sentence of the second paragraph as follows: This document ~~would~~ will highlight the main findings/concerns identified by the CHMP as well as potential consequences in terms of ~~development of the product~~, compassionate use programme (if applicable) and use of the product when it is already on the market.	
2nd paragraph	Depending on the circumstances, the CHMP views on an application may contain commercially confidential information. The reflection paper should not disregard this possibility. *Amend the first sentence of the second paragraph as follows:* Normally, t~~T~~he CHMP views on on application ~~cannot~~ should not be considered as "commercially confidential information" and therefore should not raise any comments from the applicant, but details on the data package and other elements of the dossier can be confidential. ~~Nevertheless, t~~The company will be provided with the "Question and Answer" document, and will have the opportunity to comment on it prior to its publication.	Not relevant. See EMEA document on principles for Deletion of commercially confidential information.
subsection "Refusal EPAR", 1st paragraph, 5th sentence	The EMEA is required by law both to ensure transparency of the regulatory procedures but also not to disclose information of the kind covered by the obligation of professional secrecy. It thus does not seem appropriate to state "that it is the EMEA responsibility whether or not to introduce the comments with regard to confidentiality aspects." *Amend the last sentence of the third paragraphs as follows:* ~~However, it should be noted that i I~~t is the EMEA responsibility to ensure compliance with the rules and principles which govern the issues of the transparency of the regulatory procedures, public access to EMEA document and the non-disclose of information of the kind covered by the obligation of professional secrecy ~~whether or not to introduce the comments with regard to confidentiality aspects~~.	Wording clarified in line with the reflection paper on withdrawal of marketing authorisation applications.
1st paragraph, last sentence	Applicants should be granted a clear opportunity to comment on the Refusal EPAR priori to its publication. Not only should applicants be given clear opportunity to comment on the Refusal EPAR prior to its publication, these comments – especially when concerning the	See comment above

	commercial confidentiality of information – should be seriously considered and where appropriate implemented before the Refusal EPAR is published. *Amend the last sentence of the first paragraphs as follows:* The applicant will be given the opportunity to comment on the draft Refusal EPAR. It will also be provided with the final Refusal EPAR for information prior to its publication.	
subsection "Refusal EPAR", 2nd paragraph, new sentence	The preparation of the EPAR update will be subject to the same rules as the preparation of the Refusal EPAR, but this is not clarified in the reflection document. Any ambiguity should be avoided with regard to the protection of commercially confidential information. *Add the following at the end of 2nd paragraph:* The EPAR update will be prepared as the Refusal EPAR. Thus, the applicant will be given the opportunity to delete commercially confidential information, and it will be provided with the draft EPAR update for comments and with the final text prior to its publication.	Agreed, it will be made clear that the preparation of the EPAR update will follow the same procedure as the preparation of the Refusal EPAR.
new subsection	As indicated above, because of the sensitive nature of the information contained in applications for marketing authorisation, applicants should be closely involved in preparing documents (e.g., Q&A, Refusal EPAR) for publication. There should also be a specific procedure in case the applicant and the EMEA disagree as to whether information is indeed "commercially confidential". Such recourse is most relevant where the CHMP views on the application or the Refusal EPAR (or update EPAR) contain information that if published could be detrimental to the applicant as undue publication cannot be undone. The procedure may, of course, delay the publication of the Q&A and the Refusal EPAR (or update EPAR). However, Regulation 726/2004 does not impose a timeframe for providing the information on a negative opinion and refusal of marketing application, and the public is informed immediately about the negative opinion or the refusal by the EMEA press release. Also, it should be stressed that it is the EMEA responsibility to ensure compliance with the rules and principles	It is now clearly stated in this reflection paper on publication on negative opinion and refusal that the Principles to be applied for the Deletion of Commercially Confidential Information for the Disclosure of EMEA Documents (EMEA/45422/2006) are applicable to EMEA publication on negative opinion and refusal. EMEA will apply internal rules to ensure that EMEA principles for deletion of commercially confidential information are applied.

	which govern the issues of the transparency of the regulatory procedure and public access to EMEA document. *Add a subsection that reads as follows:* **Commercially confidential information** Comments given by the applicant with regard to commercially confidential information will be assessed carefully. Where the applicant and the EMEA disagree as to whether information is "commercially confidential", the disagreement will promptly be referred to a separate EMEA panel chaired by the Legal Sector of the EMEA, which will take a final decision. It is the EMEA responsibility to ensure compliance with the rules and principles which govern the issues of the transparency of the regulatory procedures, public access to EMEA document and the non-disclosure of information of the kind covered by the obligation of professional secrecy.	
"Q&A" document, 2nd paragraph	The document mentions that "the Company…will have the opportunity to comment on it prior to its publication" but no timeline is stated to receive this document.	Timeline has been added.
Refusal EPAR	The next point in the document states the timeline (10 days in this case) for receiving the document, so maybe a timeline could be included for the "Q&A" document.	Timeline has been added.

6 – Starting date of the implementation		
Line no[4]. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
[EFPIA] p. 3/6	It is disappointing that the EMEA has published this reflection paper for consultation **after** having already published information	Starting date of the implementation: As of 20 November 2005 when the relevant provisions of Regulation (EC) No 726/2004 became applicable.

[4] Where available

	on refusals, apparently in line with the paper's "draft" recommendations: i.e. after already publishing Q&A documents. It would have been preferable for the EMEA to take an approach that was more clearly in line with the requirements of Article 12(3), before allowing interested parties the opportunity to comment on their proposals. This section should be removed as it is retrospective and redundant	

ANNEX		
Line no[5]. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
[EFPIA] p. 4/6 "In case of request for re-examination"	As a re-examination may conclude that the negative opinion should be overturned, it should be made clearer that this text is only for inclusion in case if a completed re-examination procedure that confirms the initial refusal. Suggest modify as follows: "*In case of* ***completed*** ~~*request for*~~ *re-examination* ***confirming refusal****:"*	Wording revised
[PhRMA] third paragraph on page 4 ("*In all cases, add* …")	<u>If</u> the first change suggested above, *i.e*., change to Section 3, 1st bullet point, is accepted -- In implementation of that change, the second sentence should be deleted. <u>If</u> the first change suggested above, *i.e*., change to Section 3, 1st bullet point, is not accepted -- It is important to stress that an initial opinion is preliminary as it could otherwise result in premature conclusions. This is of specific relevance in case of negative opinions. *In implementation of the change to Section 3, 1st bullet point,*	New templates have now been prepared for the different scenari in case of request of re-examination or not.

[5] Where available

	amend the second sentence as follows: ~~They may request a re-examination of the opinion within 15 days of receipt of this negative opinion.~~ *Complete the second sentence as follows:* They may request a re-examination of the opinion within 15 days of receipt of this negative opinion, which thus only reflects preliminary conclusions.	
third paragraph on page 5 ("**What documentation did …**")	This section may be the most relevant with regard to commercially confidential information and it is important to stress the need to avoid improper disclosure. It is especially important not to release confidential information on the development program of a new medicinal product. Information on clinical development is considered part of innovation of a medicinal product and, as such, should not be revealed to competitors. Where necessary to release information on clinical trials, disclosure should be limited as foreseen by Directive 2001/20/20 on Clinical Trials. *Add the following sentence at the end:* *Special attention will be given to exclude any commercially confidential information, such as information on clinical development..*	EMEA principles for deletion of commercially confidential information will apply.
fourth paragraph on page 5 ("**What were the major concerns …**")	Very often, a negative opinion is not based on a final negative conclusion but rather on insufficient positive data or the inconclusive nature of the entire data package. It is important to remind the public that the conclusion may be different when new data become available. This will strengthen the wording "[a]t this point in time" that is already included in the template. *Add the following sentence at the end:* The opinion is based on the available data end new data that may become available in the future could possibly result in a different assessment.	EMEA is of the opinion that the current wording is sufficient.