European Medicines Agency
Pre-authorisation of medicines for Human Use

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON PROCEDURES FOR RE-EXAMINATION OF CHMP OPINIONS

Table 1: Organisations that commented on the draft 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	E.F.P.I.A. / Contact person: MariannePoulmaire@efpia.org	
2	Merck Sharp & Dohme (Europe) Inc.	Belgium
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Table 2:Discussion of comments

GENERAL COMMENTS - OVERVIEW
E.F.P.I.A The procedural guidance provided regarding this important regulatory option is considered very useful. However, certain sections would benefit from greater detail and/or clarification. An important task for the EMEA will be to guarantee that the applicant/MAH is given a fair chance to prepare, present and explain his view to all involved scientific bodies. In this regard, it will be key to ensure that the applicant/MAH is properly informed during all steps of the procedure. In particular, this applies where there is involvement of expert groups like SAGs or ad hoc expert groups. Although we understand the MAH/applicant will be permitted to address the CHMP at the final stage of the procedure, it will equally be important for the applicant/MAH to be given earlier opportunities to present his argumentation via direct participation or input to SAG/ad hoc expert group meetings.

SPECIFIC COMMENTS ON TEXT

1 Purpose

Line no.[1] + paragraph no.	Comment and Rationale	Outcome
Paragraph 1 p. 2/6	**E.F.P.I.A** In addition to providing a better guarantee for applicants/MAH's rights, the re-examination procedure should ensure that products are available to patients in a timely manner where this is supported by adequate Quality, Safety & Efficacy information. **Proposed change (if applicable):** This additional element should be added to the first paragraph. *"Furthermore the re-examination procedure should ensure that products are available to patients in a timely manner where this is supported by adequate Quality, Safety & Efficacy information."*	Not implemented: Ensuring that products are available to patients in a timely manner is a principle that should be ensured during the main evaluation, leading to the initial opinion, and which depends on the submission of adequate Quality, Safety & Efficacy information by the applicant/MAH.

2 Legal basis for re-examination

Line no.[2] + paragraph no.	Comment and Rationale	Outcome
Paragraph 1 p. 2/6 and 1st bullet point on p. 3/6.	**E.F.P.I.A** Although the legal basis for re-examination is relevant in the context, we believe that the expansive text in Section 2 would be more appropriately positioned in an Appendix.	Not implemented: This format is in line with the procedure for EU guidelines and related documents withihn the pharmaceutical legislative framework (EMEA/P/24143/04)

[1] Where applicable
[2] Where applicable

Section 2 "Other references" 3rd bullet point p. 3/6	**E.F.P.I.A** A general reference to SAG Mandates, Objectives and Rules for procedure would be perfectly adequate. Moreover, naming the individual SAGs would necessitate updating with the introduction of further SAGs (example: cardiology SAG, Nervous system SAG are not included in this draft). **Proposed change (if applicable):** Change to: *"The Mandate, Objectives and Rules of procedure for CHMP Scientific Advisory Groups in different therapeutic areas can be found at the EMEA website (http://www.emea.eu.int)."*	Agreed.

4 Timing of re-examination procedure		
Line no.[3] + paragraph no.	**Comment and Rationale**	**Outcome**
Section 4.2 Paragraph 2 p. 4/6	**E.F.P.I.A** The current text is ambiguous regarding whether a new co-rapporteur will be appointed for re-assessment procedures. Given the nature of the procedure, it is important to ensure a predictable and transparent approach to all re-examination cases. Since a new rapporteur shall be appointed by the CHMP it seems more logical to always change the co-rapporteur as well. **Proposed change (if applicable):** Change last sentence to: *"During the CHMP meeting following receipt of the applicant's/MAH's written notice to the Agency that he wishes to request a re-examination of the opinion, the CHMP appoints a different rapporteur and a different co-rapporteur from those appointed for the initial opinion. "*	Agreed (see below)

[3] Where applicable

	Merck Sharp & Dohme (Europe) Inc MSD recommends clarifying the cases, when a different Co-Rapporteur is appointed. **Proposed change (if applicable):** "During the CHMP meeting following the receipt of the applicant/MAHs written notice to the Agency that he wishes to request a re-examination of the opinion, the CHMP appoints a different rapporteur and, <u>for opinions where a co-rapporteur was involved in the evaluation</u> ~~where necessary~~, a different co-rapporteur from those appointed for the initial opinion."	Agreed. Based on Article 11 of the CHMP Rules of Procedure (EMEA/CHMP/111481/2004): *"For the implementation of the procedures for the re-examination of opinions mentioned in Article 9(2) of Regulation (EC) No 726/2004, in Article 32(4) of Directive 2001/83/EC, as amended, a different rapporteur and where previously appointed, a different co-rapporteur from those appointed for the initial evaluation, will be appointed to assess the grounds for the re-examination of opinions. This re-examination shall be made by using the best endeavours to ensure a new examination, independent from the first opinion",* The text of the re-examination guideline has been reworded: "*During the CHMP meeting following receipt of the applicant/MAHs written notice to the Agency that he wishes to request a re-examination of the opinion, the CHMP appoints a different rapporteur and, <u>for opinions where a co-rapporteur was involved in the initial evaluation, a different co-rapporteur from those appointed for the initial opinion (these rapporteurs will coordinate the evaluation for the duration of the re-examination procedure only).</u>"*
Section 4.2 Timetable General p. 4/6	**E.F.P.I.A** Given the tight timelines and critical nature of the outcome, it will be key that the EMEA shares all relevant information with the applicants/MAHs during the procedure. In particular this applies to the inclusion of, and outcome from, any additional expert involvement such as SAGs & expert groups. **[Also relates to Section 6 "CHMP assessment and final Opinion"]** **Proposed change (if applicable):**	Not implemented. For detailed rules of procedure of SAG, please refer to the Mandate, Objectives and rules of procedures for the CHMP Scientific Advisory

	Add a new paragraph at the bottom of Section 4.2: *"As a transparency measure and to allow the applicant to prepare for oral presentation(s) the applicant/MAH shall be given access to the identity & nature and timing of expert input, Joint Assessment Report, List of Questions addressed by the CHMP to expert groups and any recommendations made by these groups."*	Groups.
Section 4.2 Timetable Day 50 p. 4/6	**E.F.P.I.A** A SAG may not necessarily be consulted in all cases (i.e. if not requested by neither the applicant/MAH or the CHMP). However, if a SAG is consulted, the applicant/MAH should be informed of the outcome. **Proposed change (if applicable):** Modify Day 50 timetable sentence to: "*Approx Day 50: if applicable, SAG recommendation to CHMP (…) and to MAH/applicant for information*"	Not implemented. Please refer to the Mandate, Objectives and rules of procedures for the CHMP Scientific Advisory Groups.
Section 4.2 Timetable Day 60 p. 4/6	**E.F.P.I.A** It is indicated that the applicant/MAH oral CHMP explanation can occur as late as Day 60 (the last day of the procedure. This would leave no time in process for any further dialogue. Every effort should therefore be made to organise an oral explanation earlier in the process. Additionally, it will equally be important for the applicant/MAH to be given an opportunity to provide explanations/ clarifications (via direct participation or written input to ad hoc expert group meetings) earlier in the procedure. This suggestion is consistent with later text (section 6.1, line 18), which states "CHMP will decide whether the applicant/MAH will be invited for an oral explanation to the SAG". **Proposed change (if applicable):** Change first sentence of the last paragraph to: *"As early as possibly, but at the latest on Day 60, the applicant/MAH is given the right to an oral explanation to the CHMP. If the CHMP*	Not implemented: Each timetable depends on the specific chronology of each procedure, relative to the CHMP meeting dates. Please see comment below on section 6.1 (for paragraph 6)

	requests additional expert input during the procedure, consideration will also be given to provide the applicant/MAH with an opportunity to provide direct clarification at ad hoc expert group meetings which may be convened."	

5 Documentation to be supplied		
Line no.[4] + paragraph no.	**Comment and Rationale**	**Outcome**
Section 5.1 p. 4/6	**E.F.P.I.A** We suggest that the EMEA adds more detailed explanation on the content and format of the request for re-examination. We would expect such request to contain a critical analysis of the successive Rapporteur/Co-Rapporteur assessment reports from the company point of view and references to the relevant data. Secondly, we would assume that a general overview of the risk/benefit profile of the product from the applicant/MAH perspective would be appropriate. Please also make explicit that a request for a SAG (or an ad hoc expert committee) consultation can be included in the same request. Finally, we ask for a clarification whether SmPC changes may be proposed in the request in the interest of finding a commonly acceptable solution. **Proposed change (if applicable):** <u>It is suggested to:</u> 1. Detail content and format of the "grounds for the request" 2. Add the possibility of including an applicant/MAH request for SAG (ad hoc expert committee) consultation 3. Clarify if proposals for SmPC changes in order to meet CHMP concerns are acceptable or not.	Not implemented: 1. The "grounds for re-examination request" is the applicant`s document, its structure depends on how the applicant/MAH builds the argumentation. 2.EMEA/CHMP would appreciate if the applicant/MAH would send the request for SAG consultation as early as possible (preferably not waiting until day 60). 3.The acceptability of the SPC proposal will be assessed as part of the evaluation of each individual procedure

[4] Where applicable

Section 5.2 p. 4/6	**E.F.P.I.A** Submission of new data is not permitted. However, in some cases, a re-analysis or modified analysis of data that were available at the time of the initial opinion may be necessary in order to address certain points of the CHMP's initial opinion identified by the applicant/MAH for re-examination. It should be made clear that provision of such analyses is permitted if needed to support a re-examination (especially for referrals). **Proposed change (if applicable):** Add the following sentence to Section 5.2: *"This does not preclude the provision of new, or modified, analyses of the scientific data available at the time of the initial opinion, where this is necessary to address the points identified for re-examination."*	Not implemented: The legislation is sufficiently explicit on this issue.

6 CHMP assessment and final opinion		
Line no.[5] + paragraph no.	**Comment and Rationale**	**Outcome**
Section 6.1 Paragraph 2, p.5/6	**E.F.P.I.A** Where no SAG is available it is stated that the CHMP shall request the advice of additional available expertise, in the form of an ad hoc expert group meeting. It should be made clear that such consultation of an ad hoc group can also be at the request of the applicant/MAH in a similar manner to consultation of the SAG at the applicant/MAH's request. **Proposed change (if applicable):** Replace 'SAG' in 6.1 title and at least once in the first paragraph by: *'SAG (or ad hoc Advisory Group)'*	Title change is agreed: *`Consultation of the SAG (or ad hoc Expert Group)*

[5] Where applicable

	Consideration should also be given to the possibility of the applicant/MAH proposing additional experts (on condition these were free of conflict of interest and fully met the EMEA expert policy). **Proposed change (if applicable):** Consider the possibility of allowing the applicant/MAH to propose additional experts. **Merck Sharp & Dohme (Europe) Inc** MSD recommends including a statement that the applicant can also request advice of additional expertise in form of an ad hoc expert group for therapeutic areas where no SAG exists. Although not specifically provided for, we believe that this proceeding would be logical and consistent with the spirit of the legislation. In addition, we would like to propose that experts could be suggested for inclusion in the EMEA expert list. It is understood that such suggestions would only be considered, if the requirements of the EMEA expert policy would be met by the proposed candidate. **Proposed change (if applicable):** "In a therapeutic area where no SAG is established, the applicant/MAH and/or CHMP shall request the advice of additional available expertise, in the form of an ad hoc expert group meeting. The applicant/MAH may propose experts which could be considered for inclusion in the official EMEA expert list."	Not implemented (regarding applicant proposing experts to be added to EMEA database of experts): Outside the scope of re-examination guideline. Not implemented regarding applicant proposing experts to be added to EMEA database of experts: Outside the scope of re-examination guideline. The text has been reworded regarding consultation of an ad hoc expert group for therapeutic areas where no SAG exists : *"In a therapeutic area where no SAG is established, the advice of additional available expertise will be requested in the form of consultation of an ad hoc expert group meeting."*
Section 6.1 Paragraph 3 p. 5/6	**E.F.P.I.A** It is stated that the CHMP decides on composition of the SAG. However, the membership of each SAG is formal and pre-established. **Proposed change (if applicable):** Change the end of the 3rd paragraph to: *"…the CHMP decides on consultation of the SAG (and which SAG members will be required to participate in the procedure) and adopts a 'List of Questions'.."*	The text has been reworded: "*During the CHMP meeting following receipt of the applicant/MAHs written notice to the Agency or detailed grounds for requesting a re-examination of the opinion, the CHMP decides on consultation of the SAG and its composition (with regard to experts other than the SAG core*

		group), and the CHMP adopts a List of Questions to the SAG."
Section 6.1 Paragraph 5 p. 5/6	**E.F.P.I.A** In case of consultation of a SAG, the text states that certain documents to be provided to the SAG will be decided upon by the CHMP/rapporteur and the SAG secretary. These "optional" documents include the applicant's/MAH's detailed grounds for requesting the re-examination. We fail to understand how a SAG could reasonably be expected to provide advice on a re-examination if not informed of the applicant's grounds for requesting the re-examination and other relevant background information. The necessary background information should always be provided to the SAG. **Proposed change (if applicable):** Modify paragraph 5 as follows: *"EMEA will provide to the involved members of the SAG a copy of the List of Questions to the SAG, Additional documents to be given to the SAG include the applicant/MAH's detailed grounds, the rapporteur(s)' draft assessment report on the re-examination and the CHMP's initial opinion."*	The text had been reworded: *`The CHMP/rapporteurs and SAG secretary will decide on the additional documents given to the SAG/ad hoc experts…. `*, as this depends on the LOQ adopted by CHMP to be addressed by the SAG.
Section 6.1 Paragraph 6 p. 5/6	**E.F.P.I.A** The applicant/MAH will receive the LOQ. In order to fully understand context of the questions the applicant/MAH should also receive the assessment report on the re-examination. The value of a SAG consultation is likely to be greater if the applicant/MAH has the opportunity to fully explain and debate it's grounds for requesting a re-examination with the SAG. The CHMP should give due consideration to any request from the applicant/MAH for an oral explanation with the SAG. **Proposed change (if applicable):** Modify Paragraph 6 in order to read:	Partially implemented: *"The rapporteur`s assessment report on the re-examination and the LOQ for the SAG is also sent for information to the applicant/MAH. The CHMP will decide whether the applicant/MAH will be invited for an oral presentation to the SAG."* Regarding CHMP giving due consideration to any request from the applicant/MAH for an oral presentation with the SAG, this is implicit in the current text of the guideline. If an applicant/MAH requests attendance, the CHMP will consider the rights of the company to be invited for an oral presentation to the SAG/ ad-hoc expert group meeting.

	"The assessment report and LOQ is also sent for information to the applicant/MAH. The CHMP will decide whether the applicant/MAH will be invited for an oral explanation to the SAG, taking into account any request from the applicant/MAH for such a meeting."	
Section 6.2 Paragraph 2 p. 5/6	**E.F.P.I.A** In the list of documents annexed to the opinion, Annex A and the timetable for translations are missing. Is that intentional? These normally form part of the opinion. **Proposed change (if applicable):** If applicable, add Annex A and timetable for translations to the bullet points.	Partially implemented: • Annex A has been added, as an annex to the CHMP opinion. • The timetable is only an annex to the CHMP Opinion cover letter.
Section 6.3 Paragraph 1 p. 6/6	**E.F.P.I.A** Clarification is sought regarding the purpose of the proposed delay in final CHMP Opinion in situations of referral where re-examination has been requested by 1 of several parties. **Proposed change (if applicable):** Replace paragraph 1 by: *"If requests for re-examination are received from two or more parties, the final CHMP opinion will be delayed."*	Not implemented: Re-examination request from one party is enough to delay the opinion

7 Transparency/communication		
Line no.[6] + paragraph no.	**Comment and Rationale**	**Outcome**
Paragraph 1	**E.F.P.I.A** The initial CHMP opinion (whether positive or negative) is made publicly available almost immediately. In view of this, the proposal to acknowledge the fact that the applicant/MAH has requested a re-	

[6] Where applicable

	examination in the next CHMP press-release/monthly report (i.e. between approximately 2 and 4 weeks after the request is made) does not seem logical. **Proposed change (if applicable):** Modify sentence to read: *"At the time the Agency receives the written notice requesting a re-examination of opinion from the applicant/MAH, it will publicly issue a brief acknowledgement."* **Merck Sharp & Dohme (Europe) Inc** According to Article 12.3 of Regulation 726/2004, information about all refusals and the reasons for them shall be made publicly accessible. MSD believes that re-examinations will only be requested in cases where a negative CHMP opinion has been adopted. While we agree that for positive opinions, the Summary of Opinion is published, we suggest that a SmOp is also published for negative opinions to fulfil the legal requirements of making the reasons for the refusal "accessible". We further suggest that a Q&A document is only developed in cases where the negative opinion has an impact on public health and where it is likely that the public will benefit from more background information. In such cases, we believe that the applicant is responsible to provide such information on potential consequences in terms of the development of the product, compassionate use programmes or the use of the product already on the market. Therefore, MSD proposes that the company develops such Q&A document and provides it to EMEA. **Proposed change (if applicable):** "At the time of the initial CHMP opinion, a summary of Opinion (SmOp) will be published ~~for positive opinions, and a Q&A document for the negative opinions~~. If the negative opinion has an impact on public health, a Q&A document, including information on potential consequences in terms of the development of the product, compassionate use programmes or the use of the product already on the market, will be developed by the applicant and provided to EMEA."	Agreed. The following text has been entered in the Section 7, first paragraph of the Guideline on re-examination: "At the time the Agency receives written notice from the applicant/MAH requesting a re-examination of an opinion, it will make this information public." Not Implemented: This falls within the scope of the EMEA policy on publication of Opinions. Please refer to the "Reflection paper on Publication of Withdrawals". The text has been amended in accordance with the EMEA policy on publication of Opinions.

Section 7 Last paragraph p. 6/6	**E.F.P.I.A** In accordance with the general practice for EPARs, we want to make sure that the applicant/MAH is consulted before publication of the EPAR/Refusal EPAR to ascertain that no commercially confidential information (here as originating from the re-examination procedure) is released in the public domain. **Proposed change (if applicable):** Modify the last sentence to read: *"The EPAR/refusal EPAR will be published after the Commission Decision has been issued and after removal of any confidential information in consultation with the applicant/MAH."*	Not implemented: This falls within the scope of the EMEA policy on publication of EPARs.