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**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)**

PROCEDURAL ADVICE ON THE RE-EXAMINATION OF CHMP OPINIONS

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Comments should be provided using this [template](#) to: Monika.Katonova@emea.europa.eu

Note: This Procedural Advice is updated to include amendments related to the involvement of the new Committee for Advanced Therapy Medicinal products (CAT), in place since January 2009.

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1. Purpose

Re-examination procedures are meant to provide a better guarantee for applicants/MAH's rights (Recital 25 of Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency).

This document describes the procedure and gives guidance for the re-examination of different types of CHMP opinions, on the timetable for the applicants/MAHs involvement and for the assessment by CHMP, CAT (in case of Advanced Therapy Medicinal Products (ATMPs)), rapporteurs, and SAG (Scientific Advisory Group - if deemed necessary), and on the documentation to be supplied.

2. Legal basis for re-examination

Centralised Procedures

- According to Article 9 (2) of Regulation (EC) No 726/2004:

“Within 15 days after receipt of the opinion referred to in paragraph 1, the applicant may give written notice to the Agency that he wishes to request a re-examination of the opinion. In that case, the applicant shall forward to the Agency the detailed grounds for the request within 60 days after receipt of the opinion.

Within 60 days following receipt of the grounds for the request, the said Committee shall re-examine its opinion in accordance with the conditions laid down in the fourth subparagraph of Article 62(1). The reasons for the conclusion reached shall be annexed to the final opinion.”

- According to Article 62(1) of Regulation (EC) No 726/2004:

“ If there is a request for re-examination of one of its opinions, the Committee concerned shall appoint a different rapporteur and, where necessary, a different co-rapporteur from those appointed for the initial opinion. The re-examination procedure may deal only with the points of the opinion initially identified by the applicant and may be based only on the scientific data available when the Committee adopted the initial opinion. The applicant may request that the committee consult a scientific advisory group in connection with the re-examination.”

Referral Procedures

- According to Article 32(4) of Directive 2001/83/EC, of the European Parliament and of the Council on the Community Code relating to medicinal products for human use as amended:

“Within 15 days after receipt of the opinion, the applicant or the marketing authorisation holder may notify the Agency in writing of his intention to request a re-examination of the opinion. In that case, he shall forward to the Agency the detailed grounds for the request within 60 days after receipt of the opinion.

Within 60 days following receipt of the grounds for the request, the Committee shall re-examine its opinion in accordance with the fourth subparagraph of Article 62(1) of Regulation (EC) No 726/2004. The reasons for the conclusion reached shall be annexed to the assessment report...”

Variation Procedures

- Article 6(9) of Commission Regulation (EC) No 1085/2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products falling within the scope of Council Regulation (EEC) No 2309/93

establishes that: “Article 9(1) and (2) of Regulation (EEC) No 2309/93 shall apply to the opinion adopted by the competent Committee.” The Articles quoted (which since 20 November have been replaced by Article 9(1) and (2) of Regulation (EC) No 726/2004) establish the general procedure for the CHMP opinions and re-examination of CHMP opinions.

- According to Article 2 of Commission Regulation (EC) No 1085/2003, an application for an extension shall be evaluated in accordance with the procedures set out in Articles 6 to 10 of Regulation (EEC) No 2309/93 for medicinal products for human use. These Articles cover the re-examination procedure.

Advanced Therapy Medicinal Products

According to Article 8(1) of Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004:

“The Committee for Medicinal Products for Human Use shall consult the Committee for Advanced Therapies on any scientific assessment of advanced therapy medicinal products necessary to draw up the scientific opinions referred to in Article 5(2) and (3) of Regulation (EC) No 726/2004. The Committee for Advanced Therapies shall also be consulted in the event of re-examination of the opinion pursuant to Article 9(2) of Regulation (EC) No 726/2004.”

Other references

- Notice to Applicants
[The guidance provided in the Notice to Applicants will be reviewed in accordance with the revised Regulation and Directive.]
- Committee for medicinal products for human use rules of procedure (EMEA/CHMP/111481/2004).
- Mandate, Objectives and rules of procedures for the CHMP Scientific Advisory Groups (published at the EMEA website: <http://www.emea.europa.eu>).

3. Scope

The re-examination procedure as described in this guideline is applicable to:

- CHMP opinions on applications concerning medicinal products for human use falling within the scope of Regulation (EC) No 726/2004:
 - Granting of new marketing authorisations or extensions (Article 9.2)
 - Renewal (Article 14.2)
 - Annual reassessment (Article 14.8)
 - Scientific opinions for evaluation of medicinal products outside the Community after consulting the WHO (Article 58)
- CHMP opinions on referrals falling within the scope of Article 32.4 of Directive 2001/83/EC, as amended.
- CHMP opinions on type II variations and extension applications falling within the scope of Commission Regulation (EC) No 1085/2003 (Article 6.9 and Article 2 respectively).
- CHMP opinions in the framework of the evaluation procedure for the approval of Advanced Therapy Medicinal Products under Article 8(1) of Regulation (EC) No 1394/2007.

The re-examination procedure is not applicable to the following procedures:

- Type 1A and type IB variations.
- Compassionate use (Article 83.4)
- Scientific recommendation on classification of Advanced Therapy Medicinal Products (Article 17 of Regulation (EC) No 1394/2007).
- Certification of Advanced Therapy Medicinal Products (Article 18 of Regulation (EC) No 1394/2007).

4. Timing of re-examination procedure

4.1. Timetable for the applicant/MAH:

Within 15 calendar days (=sending date by applicant/MAH as documented by fax/ eudralink/registered mail) after receipt of the opinion (=receipt date by applicant/MAH as documented by fax/ eudralink/registered mail), the applicant/MAH may give written notice to the Agency that he wishes to request a re-examination of the opinion.

Within 60 calendar days after receipt of the opinion the applicant/MAH forwards to the Agency detailed grounds for requesting re-examination.

4.2. Timetable for the assessment

General principles:

Within 60 calendar days following receipt of the grounds for the request, the CHMP shall re-examine its opinion. This re-examination shall be done after consultation of the CAT, in case of a medicinal product falling within the definition of an ATMP according to Article 2 of Regulation (EC) No 1394/2007. The detailed timetables (1 and 2) presented below -as a guidance- will depend on, amongst others, the date of receipt of the detailed grounds for the request of re-examination vis-à-vis the CHMP, CAT meeting dates, as appropriate. However, it will never exceed 60 calendar days (i.e. no clockstop).

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 their Assessment Teams and, for opinions where a co-rapporteur was involved in the initial evaluation, a different co-rapporteur and its assessment team from those appointed for the initial opinion (these rapporteurs and their assessment team Members will coordinate the evaluation for the duration of the re-examination procedure only). At this meeting the CHMP may have preliminary discussions on consultation and composition of the SAG; if possible adopts a draft List of Questions to SAG at the same meeting.

For ATMPs, 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 CAT **Rapporteur and Assessment Team** and a different **CHMP Coordinator** and, for opinions where co-rapporteurs were involved in the initial evaluation, a different CAT co-rapporteur **and Assessment Team** and a different **CHMP Coordinator** from those appointed for the initial opinion (these rapporteurs and their assessment team Members will coordinate the evaluation for the duration of the re-examination procedure only). At this meeting the CHMP and/or CAT may have preliminary discussions on consultation and composition of the SAG; if possible adopts a draft List of Questions to SAG at the same meeting

A/ Calculation of timetable 1:

- Day 0: receipt by EMEA of Applicant/MAH's detailed grounds for the request of re-examination
- Day 1: the next calendar day
- Approx. Day 30: Circulation of rapporteur(s)' assessment report(s) to CHMP (including draft LOQ to SAG, if applicable).
- Approx. Day 40: CHMP comments
- Approx. Day 45: Joint assessment report (including revised LOQ to SAG if applicable)
- Approx. Day 50: if applicable, SAG recommendation to CHMP (through SAG meeting or written procedure)

At the latest on Day 60: The applicant/MAH is given the right to an oral explanation to the CHMP; CHMP adopts opinion (reasons for the conclusion reached shall be annexed to the final opinion). Where the last day of a period is a public holiday/ Saturday/Sunday, the period shall end with the expiry of the last hour of the following working day.

B/ Calculation of timetable 2 only in case of an advanced therapy medicinal product, where CHMP must consult the CAT:

Since, in case of an Advance Therapy Medicinal Product, both the CAT and the CHMP will be involved in this re-examination procedure, and eventually a SAG consultation may take place within such very tight legal timeframe, the Applicant/MAH, is strongly advised to contact the PTL to discuss the most appropriate dates for submission of the notification and the grounds for re-examination, within the legal timeframe, to accommodate, as much and as far as possible meeting schedules dates.

The Applicant/MAH is also informed that some part/most of this procedure may take place by writing procedure. Consequently, in case the Applicant/MAH wishes to be heard before the Committees, such request must be done as early as possible in the process.

- Day 0: receipt by EMEA of Applicant/MAH's detailed grounds for the request of re-examination
- Day 1: the next calendar day
- Approx. Day 30: CAT Rapporteurs and their assessment Teams Members in collaboration with CHMP Coordinators draft the assessment report(s) and circulate them to both CAT and CHMP (including draft LoQ to SAG, if applicable).
- Approx. Day 40: CAT and CHMP comments
- Approx. Day 45: draft joint CAT Rapporteur and CAT Co-Rapporteur assessment report (including revised LoQ to SAG if applicable)
- Approx. Day 50: if applicable, SAG meeting/oral explanation and recommendation sent to CAT and CHMP.
- Approx Day 55, oral explanation at the CAT and/or adoption of draft opinion by CAT, for final approval of the CHMP.
- At the latest by approx. Day 60, oral explanation at CHMP and adoption of final CHMP opinion.

At the latest on Day 55: The applicant/MAH is given the right to an oral explanation in front of the CAT before it adopts its draft opinion.

This draft opinion of the CAT includes the reasons for the conclusion reached at CAT level, taking into account, as appropriate the SAG recommendations. All this being annexed to the final draft opinion adopted by the CAT before being transmitted to the CHMP in a timely manner, who is ultimately responsible for the adoption of the CHMP opinion. Where the last day of a period is a public holiday/ Saturday/Sunday, the period shall end with the expiry of the last hour of the following working day.

5. Documentation to be supplied.

The applicant/MAH shall forward to the Agency the detailed grounds for the request for re-examination of the opinion. As stated in Article 62.1 paragraph 4 of Regulation 726/2004 and Article 32.4 paragraph 3 of Directive 2001/83/EC, as amended, *“the re-examination procedure may deal only with the points of the opinion initially identified by the applicant/MAH and may be based only on the scientific data available when the Committee adopted the initial opinion.”*

In case, the applicant requests that the committee consults a SAG in connection with the re-examination, the applicant should inform the CHMP and CAT, in case of an ATMP, as soon as possible of this request. The request should also be mentioned in the notification letter and in the cover letter submitted with the grounds for the request for re-examination.

Thus the rule for re-examinations in MA applications procedures and referrals is that only scientific data available when the Committee adopted the initial opinion is admissible at the re-examination stage.

6. CHMP assessment and final opinion

The general principles of coordination of the evaluation (i.e. role and interactions of rapporteur, co-rapporteur, CHMP, EMEA) will not be further detailed in this document (please refer to the guidance and procedures detailed in NTA vol. 2A, CHMP rules of procedure and Mandate, Objectives and Rules of Procedure for CHMP SAGs, CAT rules of procedure, procedural advice on evaluation of advanced therapy medicinal products). However, in view of the particularly strict timetable of re-examination procedures (as outlined above), this paragraph will provide some further detail on the involvement of SAGs in re-examination procedures.

6.1. Consultation of the SAG (or ad hoc expert group)

General principles:

The decision on consultation of the SAG for a re-examination procedure will amongst others depend on the CHMP or the applicant/MAH's request for consultation of the SAG by CHMP.

In case the applicant/MAH requests a SAG, the applicant/MAH will preferably inform the CHMP of this request as early as possible. Such request should be duly motivated. When there is no request from the applicant/MAH the CHMP will decide on the need for additional expertise. In case of a request for consultation of the SAG coming from the applicant, the CHMP will systematically consult the SAG.

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.

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 the 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.

If the LOQ to the SAG has not yet been adopted during a CHMP meeting, it will be adopted by written procedure.

EMA will provide to the involved members of the SAG a copy of the List of Questions to the SAG. The CHMP/rapporteurs and the SAG secretary will decide on the additional documents given to the SAG/ad hoc experts, e.g. the applicant/MAH's detailed grounds, the rapporteur(s)' draft assessment report on the re-examination, the CHMP's initial opinion.

The rapporteur's assessment report, as appropriate, on the re-examination and the (relevant sections of 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.

The SAG recommendation will be reflected in the CHMP assessment report.

The MAH/ applicant in any case has the right to be heard by the CHMP.

Consultation of a SAG in the case of an ATMP:

The decision on consultation of the SAG for a re-examination procedure will amongst others depend on the CAT/CHMP or the applicant/MAH's request for consultation of the SAG by CHMP.

In case the applicant/MAH requests a SAG, the applicant/MAH will preferably inform the CHMP of this request as early as possible. Such request should be duly motivated. When there is no request from the applicant/MAH the CHMP/CAT will decide on the need for additional expertise. In case of a request for consultation of the SAG coming from the applicant, the CHMP/CAT will systematically consult the SAG.

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.

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 and the CAT decide, as appropriate, on the consultation of the SAG and its composition (with regard to experts other than the SAG core group), and the CHMP/CAT, as appropriate adopts a List of Questions to the SAG.

If the LOQ to the SAG has not yet been adopted during a CHMP/CAT meeting, it will be adopted by written procedure.

EMA will provide to the involved members of the SAG a copy of the List of Questions to the SAG. The CHMP/CAT rapporteurs and the SAG secretary will decide on the additional documents given to the SAG/ad hoc experts, e.g. the applicant/MAH's detailed grounds, the rapporteur(s)' draft assessment report on the re-examination, the CHMP's initial opinion, the draft CHMP opinion prepared by the CAT.

The draft CHMP assessment report and the CHMP assessment report on the re-examination and the (relevant sections of the) LOQ for the SAG is also sent for information to the applicant/MAH. The CHMP/CAT, as appropriate will decide whether the applicant/MAH will be invited for an oral presentation to the SAG.

The SAG recommendation will be reflected in the draft opinion adopted by the CAT and ultimately also in the CHMP assessment report.

The MAH/ applicant in any case has the right to be heard by the CHMP and/or CAT.

6.2. CHMP final opinion on re-examination

Within 15 calendar days after its adoption, the Agency shall send the final CHMP opinion to the Commission, to the Member States and to the applicant/MAH.

If an opinion is favourable to the granting maintenance of the MA, the following documents shall be annexed to the opinion:

- Annex A
- Draft SPC, PL and labelling
- Details of conditions affecting the authorisation (supply)
- Details of recommended conditions or restrictions with regard to the safe and effective use of the medicinal product

The CHMP assessment report is appended to the CHMP opinion together with the draft opinion prepared by the CAT, in case of an ATMP.

If an opinion is not favourable to the granting/maintenance of the MA, the following document shall be annexed to the opinion:

- Scientific conclusions and grounds for the refusal of the granting of the Marketing authorisation.

The CHMP assessment report is appended to the CHMP opinion together with the draft opinion from the CAT, in case of an ATMP.

6.3. Special situations

In case of re-examination request by 1 of several parties, the final CHMP opinion will be delayed for all parties involved in the referral.

In case of withdrawal (by applicant/MAH) of the request for re-examination, the initial CHMP opinion will immediately become the final CHMP opinion.

7. Transparency/communication

At the time of the initial CHMP opinion, a Summary of Opinion (SmOp) will be published for positive opinions, and a Question & Answer document for the negative opinions, including in case of an ATMP a summary of the draft opinion from the CAT and any divergences between such draft opinion from the CAT and the CHMP final opinion.

The start of a re-examination procedure will be mentioned in the CHMP Monthly Report.

At the end of the re-examination procedure, the SmOp/Questions & Answer document of the initial opinion will be revised to reflect the outcome of the re-examination procedure, and will be published at the time of the CHMP press release/CHMP Monthly Report.

In case of positive outcome, the EPAR will be published once the Commission Decision has been issued.

In case of withdrawal by the applicant/MAH during the re-examination process, information about the withdrawal will be published by the EMEA.

In case of refusal following the re-examination process, information about the refusal will be published.