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Procedural advice on the evaluation of advanced therapy medicinal product in accordance with Article 8 of Regulation (EC) No 1394/2007

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Table of Content

Table of Content	2
1. Introduction	3
2. Scope	3
3. Legal basis	3
4. Composition of the assessment teams and appointment of Rapporteurs	5
5. Roles and responsibilities of all interested parties involved in the evaluation procedure for ATMPs	6
5.1 General Principles.....	6
5.2 Role of the CAT	7
5.3 Role of the CAT (Co-)Rapporteurs.....	8
5.4 Role of the peer reviewers and CAT members	8
5.5 Role of the CHMP.....	8
5.6 Role of the CHMP Coordinators	9
5.7 Role of the peer reviewers and CHMP members	9
5.8 Role of the PRAC, PRAC (Co-)Rapporteurs and PRAC members	9
5.9 Role of the EMA.....	10
5.10 Role of the Scientific Advisory Group (SAG) or ad hoc expert group	10
5.11 Role of the Working Parties (WPs)	10
6. Timetable of the assessment:	11
6.1 Standard timetable for the evaluation of an Advanced Therapy Medicinal Product (ATMP) for initial marketing authorisation application under the centralised application ..	11
6.2. Accelerated Assessment:	15
7. Withdrawal of MAA	15
8. Re-examination of the opinion	15
Abbreviations	17
References	17

1. Introduction

Advanced Therapy Medicinal Products (ATMPs) are medicinal products for human use, including gene therapy, somatic cell therapy and tissue engineered products. ATMPs may also incorporate, as an integral part of the product, one or more medical devices, in which case they are referred to as “Combined ATMPs” as defined in Article 2 of the Regulation (EC) No 1394/2007 on Advanced Therapy Medicinal Products.

As provided for in the ATMP Regulation (EC) No 1394/2007, the scientific evaluation of Marketing Authorisation Applications (MAAs) for ATMPs is primarily performed by the Committee for Advanced Therapies (CAT). The CAT prepares a draft opinion on the quality, safety and efficacy of each ATMP subject to marketing authorisation application (MAA) which is sent for final approval to the Committee for Medicinal Products for Human Use (CHMP). The CHMP recommendation is then sent to the European Commission, which adopts a decision binding in all Member States.

2. Scope

This document describes the procedure for the evaluation of marketing authorisation applications for ATMPs.

This procedure is put in place to establish timely and effective interactions between the EMA and the different committees (CAT, CHMP and the Pharmacovigilance Risk Assessment Committee (PRAC)) in conjunction with the Applicant during the centralised evaluation of an ATMP.

The CAT is also responsible for post-authorisation activities of ATMPs. Though not described in this document, the same principles as outlined for the MAA evaluation procedure applies to post-authorisation activities (e.g. variations, renewals, etc.) according to the established timetables for the relevant procedure.

3. Legal basis

- According to Recital 10 of Regulation (EC) No 1394/2007:

“(10) The evaluation of advanced therapy medicinal products often requires very specific expertise, which goes beyond the traditional pharmaceutical field and covers areas bordering on other sectors such as biotechnology and medical devices. For this reason, it is appropriate to create, within the Agency, a Committee for Advanced Therapies, which should be responsible for preparing a draft opinion on the quality, safety and efficacy of each advanced therapy medicinal product for final approval by the Agency’s Committee for Medicinal Products for Human Use. In addition, the Committee for Advanced Therapies should be consulted for the evaluation of any other medicinal product which requires specific expertise falling within its area of competence.”

- According to Recital 11 of Regulation (EC) No 1394/2007:

“(11) The Committee for Advanced Therapies should gather the best available expertise on advanced therapy medicinal products in the Community. The composition of the Committee for Advanced Therapies should ensure appropriate coverage of the scientific areas relevant to advanced therapies, including gene therapy, cell therapy, tissue engineering, medical devices, pharmacovigilance and

ethics. Patient associations and clinicians with scientific experience of advanced therapy medicinal products should also be represented.”

- According to Recital 12 of Regulation (EC) No 1394/2007:

“To ensure scientific consistency and the efficiency of the system, the Agency should ensure the coordination between the Committee for Advanced Therapies and its other Committees, advisory groups and working parties, notably the Committee for Medicinal Products for Human Use, the Committee on Orphan Medicinal Products, and the Scientific Advice Working Party.”

- According to Article 8 of Regulation (EC) No 1394/2007:

“1. 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.

2. When preparing a draft opinion for final approval by the Committee for Medicinal Products for Human Use, the Committee for Advanced Therapies shall endeavor to reach a scientific consensus. If such consensus cannot be reached, the Committee for Advanced Therapies shall adopt the position of the majority of its members. The draft opinion shall mention the divergent positions and the grounds on which they are based.

3. The draft opinion given by the Committee for Advanced Therapies under paragraph 1 shall be sent to the Chairman of the Committee for Medicinal Products for Human Use in a timely manner so as to ensure that the deadline laid down in Article 6(3) or Article 9(2) of Regulation (EC) No 726/2004 can be met.

4. Where the scientific opinion on an advanced therapy medicinal product drawn up by the Committee for Medicinal Products for Human Use under Article 5(2) and (3) of Regulation (EC) No 726/2004 is not in accordance with the draft opinion of the Committee for Advanced Therapies, the Committee for Medicinal Products for Human Use shall annex to its opinion a detailed explanation of the scientific grounds for the differences.

5. The Agency shall draw up specific procedures for the application of paragraphs 1 to 4.”

- According to Article 20 of Regulation (EC) No 1394/2007:

“1. A Committee for Advanced Therapies shall be established within the Agency.

2. Save where otherwise provided in this Regulation, Regulation (EC) No 726/2004 shall apply to the Committee for Advanced Therapies.

3. The Executive Director of the Agency shall ensure appropriate coordination between the Committee for Advanced Therapies and the other Committees of the Agency, in particular the Committee for Medicinal Products for Human Use and the Committee for Orphan Medicinal Products, their working parties and any other scientific advisory groups.”

- According to Article 23 of Regulation (EC) No 1394/2007:

“The Committee for Advanced Therapies shall have the following tasks:

(a) to formulate a draft opinion on the quality, safety and efficacy of an advanced therapy medicinal product for final approval by the Committee for Medicinal Products for Human Use and to advise the latter on any data generated in the development of such a product;

(b) to provide advice, pursuant to Article 17, on whether a product falls within the definition of an advanced therapy medicinal product;

(c) at the request of the Committee for Medicinal Products for Human Use, to advise on any medicinal product which may require, for the evaluation of its quality, safety or efficacy, expertise in one of the scientific areas referred to in Article 21(2);

(d) to provide advice on any question related to advanced therapy medicinal products, at the request of the Executive Director of the Agency or the Commission;

(e) to assist scientifically in the elaboration of any documents related to the fulfilment of the objectives of this Regulation;

(f) at the Commission's request, to provide scientific expertise and advice for any Community initiative related to the development of innovative medicines and therapies which requires expertise in one of the scientific areas referred to in Article 21(2);

(g) to contribute to the scientific advice procedures referred to in Article 16 of this Regulation and in Article 57(1)(n) of Regulation (EC) No 726/2004."

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

"1. Where, in accordance with the provisions of this Regulation, the Committee for Medicinal Products for Human Use, the Committee on Herbal Medicinal Products or the Committee for Medicinal Products for Veterinary Use is required to evaluate a medicinal product, it shall appoint one of its members to act as rapporteur for the coordination of the evaluation. The Committee concerned may appoint a second member to act as co-rapporteur."

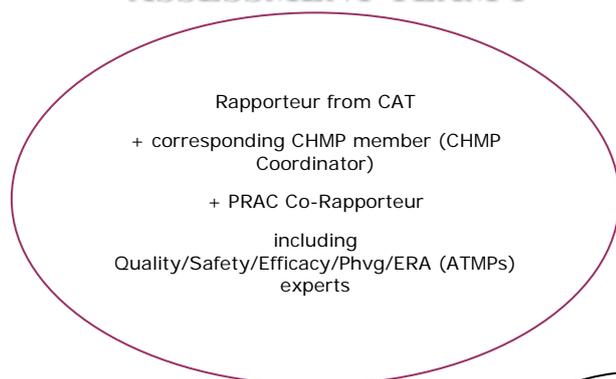
4. Composition of the assessment teams and appointment of Rapporteurs

For the evaluation of an initial marketing authorisation application for an ATMP, two assessment teams are appointed:

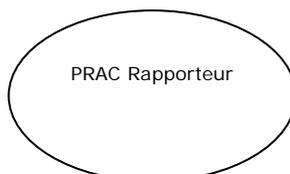
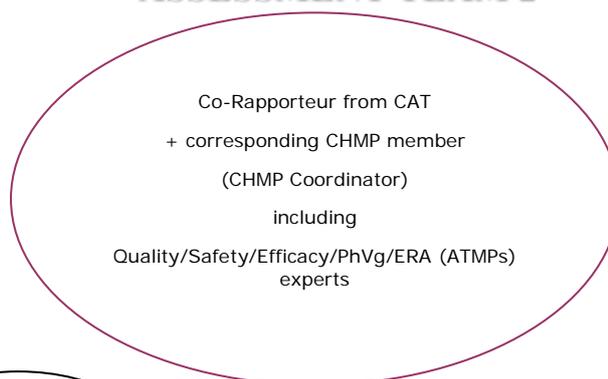
- The first assessment team consists of the CAT Rapporteur, the CHMP Coordinator and a PRAC Co-Rapporteur.
- The second assessment team consists of the CAT Co-Rapporteur and the CHMP Coordinator.

A PRAC Rapporteur is also appointed from amongst the members and alternates of the PRAC.

ASSESSMENT TEAM 1



ASSESSMENT TEAM 2



Each assessment team should include assessors with experience in the evaluation of Quality, Safety, Efficacy, Pharmacovigilance and Environmental Risk Assessment (ERA) for ATMPs.

Peer reviewers (at least one from the CAT and one from the CHMP) may be appointed from amongst the members or alternates from both Committees, if appropriate.

When a CAT Rapporteur is also a CHMP Member or alternate, no additional CHMP Coordinator is nominated in the team.

Each Committee is responsible for the appointment of its own Rapporteurs. For initial applications for ATMPs, the chairs of the CAT, CHMP and PRAC will discuss and agree on the appointment of Rapporteurs, CHMP Coordinators and peer reviewers.

The use of multinational assessment teams is strongly encouraged as a means to increase capacity, competence and collaboration in the EU regulatory system.

5. Roles and responsibilities of all interested parties involved in the evaluation procedure for ATMPs

5.1 General Principles

The lead responsibility for the assessment of marketing authorisation applications for ATMPs (and by analogy also post-authorisation activities such as variations, renewals, etc.) is with the CAT.

The milestones for the product discussion during the evaluation of a MAA for an ATMP takes place at the CAT. This includes:

- the adoption of the Day 120 List of Questions (LoQ),
- the adoption of the Day 180 List of outstanding issues (LoOI), and
- oral explanation (where required)

The CHMP Coordinators should join the CAT discussion for the product to ensure adequate interaction and information flow between the CAT and the CHMP. Similarly, the PRAC (Co-) Rapporteurs should join the CAT discussion to facilitate the information flow between the CAT and the PRAC.

Any comments of the other committees regarding the assessment of the MAA should be submitted to the CAT Rapporteurs in a timely manner. In particular, all comments to the Day 120 LoQ or Day 180 LoOI from the CHMP, PRAC, involved Working Parties (WP), Scientific Advisory Groups (SAGs), Inspections and Notified Bodies, as applicable, should be sent within the specified commenting period prior to the discussions at the CAT. After adoption by the CAT, the Day 120 LoQ and Day 180 LoOI are sent to the applicant.

The CHMP is informed by the CHMP coordinators and/or CAT (Co-)Rapporteurs of the major objections and key scientific issues as discussed by CAT. In the exceptional case that the CHMP identifies major issues with the Day 120 LoQ or Day 180 LoOI (e.g. identification of *de novo* important scientific questions), these will be added to the LoQ/LoOI in collaboration with the CAT Chair and the CAT (Co-) Rapporteurs. The updated LoQ/LoOI will be circulated to the CAT for information and sent to the applicant.

When discussing the LoOI, the CAT will consider the need for an oral explanation. The oral explanation for an ATMP takes place before the CAT. The CHMP Coordinators should attend the OE before the CAT, if possible. The CHMP Chair may also attend the OE before the CAT. In the exceptional case that the CHMP opinion deviates from the CAT draft opinion (e.g. change of outcome or conditions to the marketing authorisation, etc.), an oral explanation (upon request/agreement of the CHMP) could take place before the CHMP. In such case, the applicant/marketing authorisation holder can only present or refer to data that have been previously assessed by the CAT. In case of an oral explanation before the CHMP, the CAT Chair and the CAT (Co-)Rapporteurs are expected to attend the oral explanation to support the discussion.

The CAT (Co-)Rapporteurs should join the CHMP discussions on the draft opinion submitted by the CAT. This discussion may be also be attended by the CAT Chair/CAT Vice-Chair.

When the CHMP identifies major concerns on the draft opinion adopted by the CAT, a clarification meeting shall be organised by the EMA in advance of the CHMP plenary meeting. The CAT and CHMP chairs, the CAT (Co-)Rapporteurs, the CHMP Coordinators and the CHMP members and where applicable the PRAC members, who raised major concerns, shall participate to facilitate the resolution of emerging divergences prior to the adoption of the final CHMP opinion.

5.2 Role of the CAT

The CAT adopts the Day 120 LoQ, Day 180 LoOI, the draft opinion and decides on the request of the applicant for a clock-stop.

The oral explanation takes place before the CAT.

The CAT decides on the need to involve/consult any of the WP/SAG/Notified Bodies/Inspections and proposes the list of questions to the experts.

The CAT leads the assessment of the product in case of re-examination.

5.3 Role of the CAT (Co-)Rapporteurs

The role of the CAT (Co-)Rapporteurs is to perform the scientific evaluation of ATMPs, and to lead the discussions at the CAT. The CAT (Co-)Rapporteurs prepare the assessment report, the LoQ, the joint assessment report and the LoOI (called thereafter the milestone documents) and circulate them to the CAT, CHMP and PRAC members according to the timetable agreed for the evaluation procedure and taking into account the timeframe laid down in the relevant legislation.

The CAT (Co-)Rapporteurs should inform and liaise with the CHMP coordinators, to ensure a consistent flow of information and to facilitate discussions between the committees. Similar, discussions should take place with the PRAC (Co-) Rapporteurs as necessary.

The CAT (Co-)Rapporteurs identify the need for consultation with WP/SAG/Notified Bodies/ Inspections involvement at Day 80/Day 150 in preparation of the Day 120 LoQ/Day 180 LoOI.

The CAT (Co-)Rapporteurs shall take into consideration comments received from PRAC regarding the pharmacovigilance plan and the risk minimisation measures of the RMP.

In case a medicinal product for human use contains or consists of genetically modified organisms (GMO), the CAT (Co-)Rapporteurs shall take into consideration comments received from the consultations with national competent authorities designated under Article 4(4) of Directive 2001/18/EC (GMO competent authority).

In case of a combined ATMP, the CAT (Co-)Rapporteurs shall take into consideration comments received from the consultation with the Notified Bodies (where applicable).

For re-examination procedures, different CAT (Co-)Rapporteurs are appointed and prepare the assessment report.

5.4 Role of the peer reviewers and CAT members

CAT peer reviewers review the (Co-)Rapporteurs' scientific assessment report, including the validity of the scientific/regulatory conclusions reached up to Day 120 LoQ and participate in the peer review teleconference to discuss and critically analyse the different objections and concerns raised in the Rapporteur and Co-Rapporteur assessment reports and proposed draft List of Questions.

The role of the CAT members is to provide comments, to vote and adopt the milestone documents, and to adopt the draft opinion before it is transmitted for final adoption to the CHMP.

5.5 Role of the CHMP

The CHMP is informed during its plenary meeting of the major objections and key scientific issues raised during the evaluation (at Day 120 LoQ/Day 180 LoOI) of the ATMP under review.

In the exceptional case that the CHMP identifies major issues with the Day 120 LoQ or Day 180 LoOI e.g. identification of *de novo* important scientific questions), these will be added to the LoQ/LoOI in collaboration with the CAT Chair and the CAT (Co-)Rapporteurs. The updated LoQ/LoOI will be circulated to the CAT for information and sent to the applicant.

The CAT sends the draft opinion for final approval to the CHMP. The CHMP adopts the final opinion.

In case the CHMP opinion is not in accordance with the draft opinion adopted by the CAT, the CHMP shall annex to its opinion a detailed explanation of the scientific grounds for the differences.

When a request for re-examination is received, the CHMP is responsible for the re-examination of the CHMP opinion. The re-examination of the CHMP opinion shall be based on the (new) draft opinion adopted by the CAT. In case the CHMP opinion is not in accordance with the (new) draft opinion adopted by the CAT, the CHMP shall annex to its opinion a detailed explanation of the scientific grounds for the differences.

5.6 Role of the CHMP Coordinators

The CHMP Coordinators are part of the CAT Rapporteur and Co-Rapporteur teams conducting the assessment. They are responsible for ensuring the consistent flow of information to CHMP, and in collaboration with the CAT (Co-)Rapporteurs, for the presentation of major objections and key scientific issues arising from the assessment of the MAA to the CHMP, and for guiding the final CHMP discussion at the time of the adoption of the opinion. The CHMP coordinators should participate in and contribute to the CAT discussion when possible.

The CHMP Coordinators provide input in all the relevant milestone documents and should attend the oral explanation at the CAT, if possible.

5.7 Role of the peer reviewers and CHMP members

The CHMP peer reviewers review the CAT (Co-) Rapporteurs scientific assessment report, including the validity of the scientific and regulatory conclusions reached up to Day 120 LoQ, and participate in the peer review teleconference to discuss and critically analyse the different objections and concerns raised in the CAT Rapporteur and Co-Rapporteur assessment reports and proposed draft List of Questions.

CHMP members may provide comments on the milestone documents (respecting the timeframe for comments prior to the adoption of the documents by CAT) and share any comments with the corresponding CAT member. CAT and CHMP members in each member state are encouraged to discuss any comments they have nationally and to send one consolidated list of comments (from CAT and CHMP members) per member state, when possible.

The peer reviewers and CHMP members can follow the Oral Explanation before the CAT, either in person, or via other means (video-link, teleconference, and videoconference).

5.8 Role of the PRAC, PRAC (Co-)Rapporteurs and PRAC members

The PRAC is responsible for providing recommendations to the CAT with focus on the evaluation on the pharmacovigilance plan and the risk minimisation measures of the RMP. The PRAC recommendations should be considered by the CAT when drafting the milestone documents and draft opinion.

The PRAC (Co-)Rapporteurs are responsible to provide recommendations to the CAT on matters related to the risk management of the use of human medicinal products.

PRAC members may provide comments on the milestone documents (respecting the timeframe for comments prior to the adoption of the documents by CAT). They are encouraged to discuss any comments they have nationally with their CAT and CHMP members and to send one consolidated list of comments (from PRAC, CAT and CHMP members) per member state for any pharmacovigilance related matters.

5.9 Role of the EMA

The EMA ensures that the draft opinion of the CAT is given within 200 days (not including any clock-stops for the applicant to provide answers to questions from the CAT and/or CHMP).

In case a medicinal product for human use contains or consists of GMO, the EMA manages the coordination of the consultation with the GMO competent authority during the assessment procedure.

In the case of advanced therapy medicinal products which incorporate medical devices or active implantable medical devices, ("combined ATMPs"), the EMA manages the coordination of the consultation with the Notified Body at the relevant time points of the procedure.

The EMA ensures that the opinion of the CHMP is given within 210 days (not including any clock-stops for the applicant to provide answers to questions from the CAT and/or CHMP).

The EMA Product Team prepares:

- The Committees assessment report on the basis of the CAT (Co-)Rapporteur(s)' assessment reports ensuring scientific and regulatory consistency;
- The draft and final opinions for transmission by the CAT and final approval by the CHMP, respectively.

The EMA prepares and communicates with the CAT (Co-)Rapporteurs and CHMP coordinators any relevant public information related to the outcome of the assessment of ATMPs and the withdrawal of an application submitted to the EMA.

The EMA transmits the CHMP Opinion to the Commission.

5.10 Role of the Scientific Advisory Group (SAG) or ad hoc expert group

The role of the SAGs or ad hoc expert groups is to provide, on request from the CAT, an independent recommendation on scientific and technical matters relating to products under evaluation. While views expressed by the SAG should be taken into account, the ultimate responsibility for the evaluation of the product rests within the CAT.

The CAT is leading the scientific assessment, and will propose a consultation with a SAG or ad hoc expert group, if required. The CAT will propose the list of questions to the SAG. The CAT and CHMP members in each member state are encouraged to discuss any comments they have nationally (from CAT and CHMP members) per member state, when possible. The CHMP may also propose consultation of SAG to the CAT (if possible, the suggestion should be made during the commenting period). Consultation with the SAG should be identified early in the assessment process.

The SAG or ad hoc expert group conclusions are forwarded to the Chairs of the CAT and CHMP and shared with the committees according to the timetable established to ensure that legal deadlines for the evaluation of the application are met.

5.11 Role of the Working Parties (WPs)

During a marketing authorisation application for an ATMP, the CAT consults the Biologics Working Party on the quality aspects of the medicinal product.

Other Working Parties (standing or temporary) can be consulted on any scientific issues raised during a marketing authorisation application evaluation (also applicable for any post-authorisation activities).

6. Timetable of the assessment:

Once the initial MAA is validated, the EMA starts the procedure at the monthly start date published on the EMA website. The submission deadlines and detailed procedural timetables are published on the EMA website (see, '[submission deadlines and full procedural timetables](#)').

6.1 Standard timetable for the evaluation of an Advanced Therapy Medicinal Product (ATMP) for initial marketing authorisation application under the centralised application

DAY ACTION

Day/ Milestones	Action	Responsibilities
Day 1. Start Date	Start of the procedure In the case of an ATMP containing or consisting of GMOs, the EMA will inform the GMO competent authorities of the start of the procedure and manages the coordination with the GMO competent authorities. In the case of advanced therapy medicinal products which incorporate medical devices or active implantable medical devices, ("combined ATMPs"), the EMA manages the coordination of the consultation with the Notified Body at the relevant time points of the procedure.	EMA
Day 80. CAT (Co-) Rapporteur ARs	The CAT Rapporteur and Co-Rapporteur each send their Assessment Report(s) to the CAT, CHMP Coordinators, and CHMP members and EMA. The CAT Rapporteur will focus his evaluation of the RMP on the safety specifications and the need for long-term efficacy follow-up. EMA sends the Day 80 Assessment Reports to the applicant making it clear that it only sets out their preliminary conclusions and that it is sent for information only and does not yet represent the position of the CAT.	CAT (Co-) Rapporteurs
Day 94. PRAC Rapporteur AR	PRAC Rapporteur circulates the RMP assessment report, focusing on the prospective planning aspects: pharmacovigilance plan and risk minimisation measures, and proposed RMP LoQ to CAT (Co-) Rapporteurs, CHMP Coordinators, other CAT, PRAC and CHMP Committee members and EMA. EMA sends the PRAC Rapporteur AR to the applicant for information.	PRAC Rapporteur
Day 100. CAT, CHMP and PRAC comments	CAT (Co-)Rapporteurs, CHMP Coordinators, other CAT, PRAC and CHMP Committee members (including peer reviewers) and EMA send comments.	CAT(Co-)Rapporteurs, CHMP Coordinators, CHMP, PRAC and CAT members
Day 101-104.	PRAC adopts PRAC RMP Assessment Overview and Advice for D120 LoQ.	PRAC
Day 106.	PRAC Rapporteur circulates the updated RMP AR and list of	PRAC

PRAC Rap AR	questions (PhV & RMin activities only) based on the Committee members' comments for D120 LoQ.	
Day 114. CAT List of Questions (Called "Day 120 LoQ")	<p>CAT adopts the Day 120 list of questions as well as the overall conclusions and review of the scientific data to be sent to the applicant by the EMA.</p> <p>At the latest by Day 114, the CAT adopts a request for GMP/GLP/GCP inspection, if necessary (Inspection procedure starts).</p> <p>The major objections and key scientific issues (from the LoQ) are presented to the CHMP.</p> <p>In the exceptional case that the CHMP identifies major issues with the Day 120 LoQ (e.g. identification of <i>de novo</i> important scientific questions), these will be added to the LoQ in collaboration with the CAT Chair and the CAT(Co-)Rapporteurs. The updated LoQ will be circulated to the CAT for information and sent to the applicant.</p>	<p>CAT</p> <p>CHMP Coordinators & CAT(Co-)Rapporteurs</p> <p>CHMP</p>
Clock Stop	<p>Reference is made to the CHMP Document "Time allowed for applicants to respond to questions and issues raised during the assessment of new marketing authorisation applications in the centralised procedure".</p> <p>On justified grounds, the CAT may agree to a longer clock-stop. The CHMP is informed about the clock stop.</p>	Applicant
Day 115. Restart	Submission of the responses, including revised summary of product characteristics labelling and package leaflet texts in English, and restart of the clock.	Applicant
Day 150. CAT Rapporteurs Joint AR (JAR)	<p>CAT (Co-)Rapporteurs send the Joint Response Assessment Report to CHMP Coordinators, PRAC, CAT and CHMP members and the EMA.</p> <p>There is no standalone PRAC Rapporteur AR on the RMP circulated at this stage.</p> <p>EMA sends this joint Assessment Report to the applicant making clear that it is sent for information only and does not yet represent the position of the CAT.</p> <p>Where applicable inspection to be carried out.</p> <p>EMA/QRD sub-group meeting for the review of English product Information with participation of the applicant (optional) around day 165.</p>	CAT (Co-) Rapporteurs
Day 160. PRAC comments	Comments from PRAC on Joint CAT AR	PRAC members
Day 164. CAT and CHMP comments	Comments from CAT and CHMP on Joint CAT AR	CAT and CHMP members

<p>Day 166.</p> <p>Updated PRAC Rap AR</p>	<p>The PRAC Rapporteur presents the assessment on the prospective planning aspects of the RMP and the members' comments received at the PRAC plenary.</p> <p>The PRAC Rapporteur will then liaise with the CAT (Co)-Rapporteurs to reflect the members' comments and the PRAC plenary discussion in the joint Assessment Report.</p> <p>PRAC adopts PRAC RMP Assessment Overview and Advice for D180 LoOI.</p>	<p>PRAC Rapporteur</p>
<p>Day 170.</p> <p>Updated CAT JAR</p>	<p>Updated CAT Joint AR</p>	<p>CAT (Co-) Rapporteurs</p>
<p>Day 174.</p> <p>CAT List of outstanding issues/draft opinion (Called "Day 180 LoOI")</p>	<p>CAT discussion and decision on the need for an adoption of a list of "outstanding issues" (LoOI) and/or an oral explanation by the applicant or CAT draft opinion.</p> <p>CAT adopts the LoOI as well as the overall conclusions and review of the scientific data to be sent to the Applicant by the EMA.</p> <p>Clock stop.</p> <p>The major objections and key scientific issues from the LoOI are presented to the CHMP.</p> <p>In the exceptional case that the CHMP identifies major issues with the Day 180 LoOI (e.g. identification of <i>de novo</i> important scientific questions), these will be added to the LoOI in collaboration with the CAT Chair and the CAT Rapporteurs. The updated LoOI will be circulated to the CAT for information and sent to the applicant.</p> <p>Submission of final inspection report to EMA, CAT (Co-) Rapporteurs, CHMP Coordinators by the inspections team (at the latest by day 174.).</p> <p>If there is no LoOI or oral explanation, the CAT can adopt the draft opinion and transmit it to the CHMP.</p>	<p>CAT</p> <p>CHMP Coordinators & CAT(Co-)Rapporteurs</p> <p>CHMP</p>
<p>Clock Stop</p>	<p>Reference is made to the CHMP Document "Time allowed for applicants to respond to questions and issues raised during the assessment of new marketing authorisation applications in the centralised procedure".</p> <p>On justified grounds, the CAT may agree to grant a longer clock-stop. The CHMP is informed about the clock stop.</p>	<p>Applicant</p>
<p>Day 175.</p> <p>Restart</p>	<p>Restart of the clock with submission of responses or oral explanation (if needed).</p>	<p>Applicant</p>
<p>Day 189.</p> <p>CAT JAR</p>	<p>The CAT(Co)-Rapporteurs draft a joint assessment report (including the RMP aspects), taking into account the input from CHMP Coordinators/PRAC Rapporteurs and the applicant's responses</p> <p>A PRAC discussion is not foreseen at this stage.</p>	<p>CAT (Co-) Rapporteurs</p>

Day 195. CAT, CHMP, PRAC and EMA comments	CAT, CHMP and PRAC Committee members and EMA send comments on the assessment report.	CAT, CHMP, PRAC and EMA
Day 200. Updated CAT JAR	The updated AR is circulated to the PRAC and CHMP Committee members and EMA.	CAT (Co-) Rapporteurs
Day 204. CAT opinion	CAT adopts the draft opinion and draft Assessment Report and transmits it to the CHMP.	CAT
By Day 210. CHMP opinion	Adoption of CHMP Opinion and CHMP Assessment Report (and timetable for the provision of product information translations) ¹	CHMP

After adoption of a CHMP opinion, the preparation of the annexes to the Commission Decision is carried out in accordance with the following timetable:

DAY ACTION

Day	Action	Responsibilities
215 at the latest	Applicant provides to the EMA the product information and Annex A in the 25 languages (EU official languages and Icelandic and Norwegian) and the "QRD Form 1" by Eudralink*	Applicant
229	Member States will send linguistic comments on the product information by e-mail to the applicant with a copy to the EMA product shared mailbox together with QRD Form 1	Member States
235 at the latest	Applicant provides EMA with final translations of summary of product characteristics, Annex II, labeling and package leaflet in the 25 languages (+ "QRD Form 2" and "PDF checklist") by Eudralink.	Applicant
237	Transmission of Opinion and Annexes in all EU languages to applicant, Commission and Norway and Iceland.	EMA
239-261	The Commission adopts a draft Decision and consults the Standing Committee	European Commission
By 277	Finalisation of EPAR in consultation with Rapporteur, Co-Rapporteur, CAT, CHMP and Applicant (the latter for confidentiality aspects)	EMA
277	Commission adopts a decision	European Commission

*By e-mail: grd@ema.europa.eu

¹ Day 210 CHMP discussion and decision on the need for adoption of a list of "outstanding issues" and/or an oral explanation by the applicant.

Further details on the post-opinion review of translations and forms to be used, are available in the EMA's website: "[The linguistic review process of product information in the centralised procedure – human](#)".

Once the medicinal product is authorised, one set of relevant specimen of outer and immediate packaging and package leaflet should be provided to the EMA (mock-ups and specimens) for review at the latest 15 working days before launch for each strength or for each different total content per total volume [when the strength is expressed as concentration per unit volume (x mg/ml)], pharmaceutical form and container type ('product presentation') before their marketing in the EU, as per EMA guidance on '[Checking process of mock-ups and specimens of outer/immediate labelling and package leaflets of human medicinal products in the centralised procedure](#)'.

6.2. Accelerated Assessment:

The principles for the accelerated assessment procedure in accordance with Article 14(9) of Regulation (EC) 726/2004 also apply for ATMPs as per the "guideline on the Procedure for Accelerated Assessment Pursuant to Article 14 (9) of Regulation (EC) No 726/2004".

In case of Advanced Therapy Medicinal Product (ATMP)s, the CAT decides on the accelerated assessment request. The timetable will be arranged to include the review by the Committee for Advanced Therapies.

The initial assessment phase will last 120 days similarly to the standard marketing authorisation procedure; the second phase of assessment will last 30 days - the timetable therefore is 120 + 30 days.

7. Withdrawal of MAA

Where an applicant decides to withdraw their application before a draft opinion or an opinion has been adopted respectively by the CAT or CHMP or during the re-examination process, the applicant shall communicate its reasons for doing so to the EMA.

The EMA shall make this information publicly accessible and shall publish the assessment report, if available, after deletion of all information of a commercially confidential nature (as justified by the applicant).

8. Re-examination of the opinion

The principles for re-examination are outlined in "The procedure and timetables to be followed are presented in the document "Procedural advice for Re-examination of CHMP opinions (EMA/CHMP/50745/2005)".

Within 60 calendar days following receipt of the grounds for the request of a re-examination, the CHMP in consultation with the CAT is responsible for the re-examination of its opinion. In that regard, the re-examination of the CHMP opinion shall be based on the (new) draft opinion adopted by CAT.

For the re-examination, the same principles as for the initial appointment of (Co-)Rapporteurs will be followed. A different CAT Rapporteur and Assessment Team and a different CHMP Coordinator are appointed. 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 are also appointed (these Rapporteurs and their assessment team members coordinate the evaluation for the duration of the re-examination procedure only).

Following the request for re-examination, the CAT may have preliminary discussions on consultation and composition of the SAG; and if possible adopts a draft List of Questions to the SAG. The CHMP may also propose consultation of SAG to the CAT for the re-examination.

Abbreviations

This document contains a number of abbreviations, a list of which is provided here below:

- ATMP: Advanced Therapy Medicinal Products
- CAT: Committee for Advanced Therapies
- CAT (Co-)Rapporteurs: means the CAT Rapporteur and the CAT Co-Rapporteur
- CHMP: Committee for Medicinal Products for Human Use
- CHMP Coordinators: means two CHMP Members and/or CHMP Alternates
- EC: European Commission
- EMA: European Medicines Agency
- ERA: Environmental Risk Assessment
- LoOI: List of Outstanding Issues
- LoQ: List of Questions
- Milestone documents: are the assessment report, the List of Questions (LoQ), the joint assessment report and the List of Outstanding Issues (LoOI)
- OE: Oral Explanation
- SAG: Scientific Advisory Group
- WPs: Working Parties

References

- Time allowed for applicants to respond to questions and issues raised during the assessment of new marketing authorisation applications in the centralised procedure.
- [The linguistic review process of product information in the centralised procedure – human](#)
- Guideline on the Procedure for Accelerated Assessment Pursuant to Article 14 (9) of Regulation (EC) No 726/2004.
- Procedural advice for Re-examination of CHMP opinions.
- Guideline on safety and efficacy follow-up and risk management of advanced therapy medicinal products.
- Procedural Advice on CHMP/CAT/PRAC Rapporteur/Co-Rapporteur appointment principles, objective criteria and methodology in accordance with Article 62 (1) of Regulation (EC) No 726/2004.
- Consultation of environmental competent authorities on genetically-modified organisms with respect to environmental risk assessment in product evaluation (human use)
- Procedural advice on the consultation of notified bodies in the case of a combined ATMPs

- CAT Rules of procedure.
- CHMP Rules of procedure.
- PRAC Rules of procedure.