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

London, 31st March 2009
EMEA/630043/2008

COMMITTEE FOR ADVANCED THERAPIES (CAT)

PROCEDURAL ADVICE ON THE EVALUATION OF ADVANCED THERAPY MEDICINAL PRODUCT IN ACCORDANCE WITH ARTICLE 8 OF REGULATION (EC) NO 1394/2007

DISCUSSION AT CAT	January 2009
DISCUSSION AT CHMP, CAT	February-March 2009
ADOPTION BY CAT	March 2009
ADOPTION BY CHMP	March 2009
RELEASE FOR EXTERNAL CONSULTATION	April 2009
DEADLINE FOR COMMENTS	6th July 2009
ADOPTION BY CAT	
ADOPTION BY CHMP	

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Note: An update of this document will be available to explain in more details post-authorisation activities.

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1. Introduction

This scientific evaluation of Advanced Therapy Medicinal Products (ATMPs) is to be done primarily by the Committee for Advanced Therapies (CAT), which has been established by Regulation (EC) No 1394/2007. (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2007_1394/reg_2007_1394_en.pdf).

This document describes the interactions, the roles and responsibilities of the CAT, the Committee for Human Medicinal Products (CHMP) and all interested parties involved in the evaluation of ATMPs

An explanation of the evaluation process of ATMPs and the timetable is also presented.

2. Scope

This document describes the procedure and gives guidance for the steps to be followed for the evaluation of ATMPs by the applicant and the Agency. A description of how the assessment is performed by the CAT before its transmission to the CHMP for its final approval is also explained.

The draft opinion prepared by the CAT is issued on any scientific assessment of ATMPs necessary to draw up the scientific opinions by the CHMP relating to granting, variation, suspension or revocation of an authorisation to place an ATMPs on the market in accordance with Regulation (EC) No 1394/2007 and pharmacovigilance.

In view of the above, the CAT is also responsible for post-authorisation activities of ATMPs. The same principles for the evaluation procedure apply for post authorisation activities.

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:

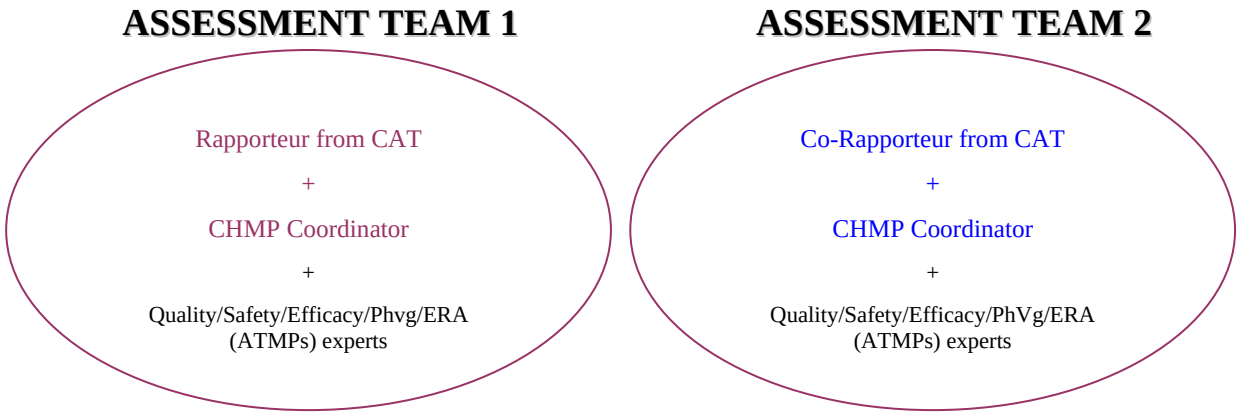
"1. The Committee for Medicinal Products for Human Use shall consult the Committee for Advanced Therapies on any scientific assessment of advanced therapy medicinal products necessary to draw up the scientific opinions referred to in Article 5(2) and (3) of Regulation (EC) No 726/2004. The Committee 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."

- 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 the CAT (Co)-Rapporteurs, Assessment Teams and CHMP Co-ordinators

For any scientific evaluation of an ATMP, the CHMP shall appoint two evaluation teams as presented below:



The first assessment team consists of the CAT Rapporteur, the CHMP Coordinator. The assessors should include Quality, Safety, Efficacy, Pharmacovigilance and Environmental Risk Assessment (ERA) experts with the appropriate ATMPs expertise.

The second assessment team consists of the CAT Co-Rapporteur, the CHMP Coordinator. The assessors should include Quality, Safety, Efficacy, Pharmacovigilance and Environmental Risk Assessment (ERA) experts with the appropriate ATMPs expertise.

Such appointment shall be made on the basis of objective criteria, which allows the use of the best available expertise in the EU on the relevant scientific area of advanced therapies. Peer reviewers (at least one from the CAT and one from the CHMP) are also appointed from amongst the members or alternates from both Committees. For such appointment, the two chairs of the CHMP and CAT discuss the appointment before their proposal is made to the CHMP. The Assessment Team identified when expressing interest for the Rapporteurship of an ATMP must include a CHMP Member as CHMP coordinator.

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

5.1 General Principles:

The CAT (Co)-Rapporteurs and CHMP Coordinators work closely together to prepare the ATMP Assessment Reports. There should be adequate interaction and communication between the two Committees, CAT and CHMP, via the Assessment Team members.

When a CAT Rapporteur is also a CHMP Member or alternate, no additional CHMP Coordinator is nominated in the team. When the CAT chair is also a CHMP member, he may undertake the function of the CHMP Co-ordinator for a procedure.

The product discussion during the evaluation of an ATMP, up to the preparation and adoption of the draft opinion, takes place at the CAT. This includes the adoption of the Day 120 List of Questions (LoQ)/ Day 170 List of outstanding issues (LoOI), involvement of Working Parties (WPs), Scientific Advisory Groups (SAGs), Inspections and Notified Bodies and Oral explanations (OE). CAT adopts the Day 120 LoQs as well as the overall conclusions and review of the scientific data to be sent to the applicant by the EMEA, taking into account, when needed remarks from CAT and CHMP Members.

The major objections and Point of interests (from both the Day 120 LoQ/Day 170 LoOI) are presented to the CHMP.

In the event that the CHMP identifies further issues for the Day 120 LoQ (i.e. upgrading to major objection or identification of *de novo* important scientific questions) the CHMP will send these issues in writing to the CAT, for the CAT to address at their next meeting.

With regard to the Day 170 LoOIs, in the event that the CHMP identifies supplementary issues (i.e. upgrade to major objection or identification of important scientific questions), such issues will be added to the LoOIs after consultation of the CAT Chair and sent to the applicant by EMEA secretariat for the applicant to address in the scheduled oral explanation which will be held in front of the CAT.

It is possible that the CHMP Coordinators join the CAT for the product discussion and that the CAT (Co)Rapporteurs join the respective CHMP discussions.

A second oral explanation could take place in front of the CHMP. In such case, the CAT Chair and the CAT (Co)-Rapporteurs are expected to attend the oral explanation to support the discussion at the CHMP.

The presentation to each Committee (CHMP and CAT) should normally be done by CAT (Co-)-Rapporteurs at CAT level and by the CHMP Coordinators at CHMP, but according to the delegations and Assessment Team Members, flexibility could be envisaged.

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

5.2 Role of the CAT:

The CAT adopts the Day 120 LoQs, Day 170 LoOIs and the draft opinion.

The oral explanation takes place in front of the CAT.

The CAT agrees on the need to involve/need for (a) WP/SAG/Notified Bodies consultation/Inspections.

5.3 Role of the CAT (Co)-Rapporteurs:

The CAT (Co)-Rapporteurs are responsible for leading the scientific evaluation and the discussion at the CAT.

The role of the CAT (Co)-Rapporteurs are to perform the scientific evaluation of ATMPs, to prepare an assessment report, the LoQ, the joint assessment report and the LoOI (called thereafter the milestone documents) and to circulate them to the CAT and CHMP 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 identify the need for WP/SAG/Notified Bodies/Inspections involvement at Day 80/Day 150 or Day 120 LoQs/Day 170 LoOIs.

For the evaluation of new marketing authorisations, Type II variation applications involving a new indication and renewals, the CAT Rapporteur is supported by the CAT Co-Rapporteur.

5.4 Role of the CAT members:

The role of the CAT members is to provide comments on the milestone documents. The CAT Members may comment on the appropriateness of WP/SAG/Notified Bodies/Inspections consultation.

They shall vote and adopt the draft opinion which will be transmitted to the CHMP.

5.5 Role of the CHMP:

As mentioned in section 4, the role of the CHMP is to appoint, under consultation of the CAT and CHMP chairs, the two evaluation teams.

The CHMP is informed during its plenary meetings of the key ATMPs scientific issues and/or divergences (at Day 120 LoQs/Day 170 LoOIs) and has the possibility to raise (further/supplementary) issues to be considered by the CAT/applicant, as described in section 5.1.

The CHMP adopts the final CHMP opinion.

When a request for re-examination is received, the CHMP is responsible for the re-examination of the CHMP opinion. The CHMP is responsible for appointing 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 in accordance with “Procedural advice on the re-examination of CHMP opinions (EMEA/CHMP/50745/2005 Rev.1).

5.6 Role of the CHMP Coordinators:

The CHMP Coordinators are responsible for ensuring the flow of information to CHMP, for the product presentation to CHMP (e.g. issues arising from Day 120 LoQ, Day 170 LoOI) and for guiding the final CHMP discussion at the time of adoption of the opinion.

The CHMP Coordinators provide input in all the relevant milestone documents.

It is possible that the CHMP Coordinators join the oral explanation at the CAT.

The CHMP Coordinators can also identify the need for WP/SAG/Notified Bodies/Inspections involvement at Day 80/Day 150 or Day 120 LoQs/Day 170 LoOIs.

5.7 Role of the peer reviewers and CHMP members:

The role of the peer reviewers and CHMP members is to provide comments on the milestone documents which are channelled via the corresponding CAT member into the CAT discussion. The peer reviewers and CHMP Members may also comment on the appropriateness of WP/SAG/Notified Bodies/Inspections consultation during the comment phase (any CHMP comments should be channelled through their CAT Member).

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

5.8 Role of the EMEA Secretariat:

The EMEA shall ensure 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 CATand/or CHMP).

The EMEA shall ensure 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 CHMP and/or CAT).

The EMEA Secretariat is responsible for ensuring full transparency of the evaluation towards the CAT and the CHMP:

The EMEA Secretariat prepares:

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

The EMEA Secretariat prepares and communicates relevant public information related to the outcome of the assessment of ATMPs and withdrawal.

5.9 Role of the Scientific Advisory Group (SAG):

Article 56(2) of the Regulation No 726/2004 and Article 27 (2) of the Regulation No 1394/2007 allow the CHMP and the CAT to establish scientific advisory groups (SAG) in connection with the evaluation of specific types of medicinal products or treatments. The role of the SAGs is to provide, on request from the CHMP and CAT, an independent recommendation on scientific and technical matters relating to products under evaluation or any other scientific issues relevant to the work of the CHMP and/or CAT. While views expressed by the SAGs are taken into account, the ultimate responsibility for final opinions rests with the CHMP.

The SAG opinion is forwarded to the Chairpersons of the CHMP and/or CAT according to the timetable established in order to ensure that legal deadlines for the evaluation of the application are met.

5.10 Role of the Working Parties (WPs):

Working Parties (standing or temporary) can be consulted by the CHMP and/or CAT on any scientific issues or during a marketing authorisation application evaluation or any post-authorisation activities.

6. Timetable of the assessment:

6.1 Start of the procedure

Once the application is validated and provided the CAT (Co)-Rapporteurs and CHMP Coordinators have confirmed that they have received the dossier (including any additional information requested during validation phase), the EMEA starts the procedure at the monthly starting date published on the EMEA website. If the CAT (Co)-Rapporteurs and the CHMP Coordinators and have not received their copies of the dossier and/or additional validation information on the day where the dossier is validated by the EMEA, the start of the procedure may be delayed until the procedural starting date of the next month.

If, within a month from the start of the procedure, any other member of the CAT and the CHMP have not received the requested parts of the dossier from the applicant, the EMEA stops the clock until confirmation is received that each member of the CAT and the CHMP have been delivered the requested documentation.

It is therefore important that applicants are able to provide a proof of delivery to CAT Co-Rapporteurs, CHMP Coordinators, and to CHMP and CAT members (upon request) to the EMEA.

Having taken into consideration the standard timetable agreed by the CHMP and the CAT for the evaluation of a centralised application, a timetable is prepared by the EMEA in consultation with the CAT (Co)-Rapporteurs and the CHMP Coordinators.

6.2 Standard timetable for the evaluation of an Advanced Therapy Medicinal Product (ATMP) under the centralised application

DAY ACTION

DAY	ACTION	Responsibilities
1.	Start of the procedure	
80.	Receipt of the Assessment Report(s) from CAT (Co)-Rapporteurs to CHMP Coordinators, CAT and CHMP members and EMEA. EMEA sends the D80 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 and CHMP.	CAT (Co)-Rapporteurs
100.	CAT (Co)-Rapporteurs, other CAT and/or CHMP members and EMEA receive comments from CHMP Coordinators, Members of the CAT and the CHMP (incl. peer reviewers).	CHMP Cooordinators, CHMP and CAT members
115.	Receipt of draft list of questions (including the recommendation and scientific discussion) from CAT Rapporteur and CAT Co-Rapporteur, as discussed with the CHMP Coordinators, peer reviewers, by CAT and CHMP members and EMEA.	CAT (Co)-Rapporteurs
120.	CAT adopts the list of questions as well as the overall conclusions and review of the scientific data to be sent to the applicant by the EMEA. The CHMP Coordinators can attend the CAT meeting during the product discussion. The major objections and Point of interests (from the LoQ) are presented to the CHMP. In the event that the CHMP identifies further issues for the LoQ (i.e. upgrading to major objection or identification of *de novo* important scientific questions) the CHMP will send these issues in writing to the CAT, for the CAT to address at their next meeting.	CAT adopts the list of questions CHMP Coordinators to present the major objections and points of interests to the CHMP
120.	At the latest by Day 120, adoption by CAT of request for GMP/GLP/GCP inspection, if necessary (Inspection procedure starts).	CAT
Clock Stop		
121*	Submission of the responses, including revised summary of product characteristics labelling and package leaflet texts in English, and restart of the clock.	Applicant

* Target dates for the submission of the responses are published on the EMEA Website (http://www.emea.europa.eu/ – Human Medicines - Application Procedures - 'Pre-SubmissionGuidance').
After receipt of the responses, the CAT adopts a timetable for the evaluation of the responses. In general the following standard timetable applies:

DAY ACTION

150.	Joint response Assessment Report from CAT (Co)- Rapporteurs received by CHMP Coordinators, CAT and CHMP members and the EMEA. EMEA sends joint Assessment Report 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 / CHMP. When applicable, Inspection to be carried out. EMEA/QRD sub-group meeting for the review of English product Information with participation of the applicant (when applicable).	CAT (Co)-Rapporteurs
160.	Deadline for comments from CAT and CHMP Members to be sent to CAT (Co)-Rapporteurs, CHMP Coordinators, EMEA and other CAT and CHMP Members.	CAT and CHMP members
170.	CAT discussion and decision onthe **need for adoption of a list of "outstanding issues"** (LoOI) and/or an **oral explanation** by the applicant. The major objections and Point of interests from the LoOI are presented to the CHMP. In the event that the CHMP identifies supplementary issues (i.e. upgrade to major objection or identification of important scientific questions), such issues will be added to the LoOIs after consultation of the CAT Chair and sent to the applicant by EMEA secretariat for the applicant to address in the scheduled oral explanation, which will be held in front of the CAT. *If an oral explanation is needed, the clock is stopped to allow the applicant to prepare the oral explanation.* Submission of final inspection report to EMEA, CAT (Co)-Rapporteurs, CHMP Coordinators by the inspections team (at the latest by day 170). **If there is no LoOI or oral explanation**, the CAT can adopt the draft opinion and transmits it to the CHMP.	CAT adopts the LoOIs CHMP/CHMP Coordinators to present the major objections and points of interests to the CHMP
171	CAT oral explanation	CAT
171	Discussion on the draft opinion and identification of the recommendations for Marketing Authorisation/refusal which will be transmitted to CHMP.	CAT
	The applicant provides the final draft of English summary of product characteristics, labeling and package leaflet, and where needed an updated Risk Management Plan and traceability system.	Applicant
180	The CHMP will discuss the Grounds for approval/refusal as adopted by CAT. The outcome of the discussions will be transmitted to the CAT via the CHMP Coordinator or the joint CAT and/or CHMP Members.	CHMP

200	CAT adopts the draft opinion and draft Assessment Report and transmits it to the CHMP.	CAT
By 210	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

215 at the latest	Applicant provides the EMEA with summary of product characteristics, Annex II, labelling and package leaflet and Annex A in the 20 languages (All EU languages including Norwegian). EMEA circulates draft translations to Member States for review.	
232 at the latest	Applicant provides EMEA with final translations of summary of product characteristics, Annex II, labeling and package leaflet in the 20 languages, taking account comments received from Member States by Day 229.	
By 237	Transmission of Opinion and Annexes in all EU languages to applicant, Commission, and Members of the Standing Committee, and Norway and Iceland.	
By 246	Applicant provides EMEA with one final full colour 'worst-case' mock-up of outer and inner packaging for each pharmaceutical form.	

Further details on the post-opinion review of translations and forms to be used, are available In the EMEA "New linguistic review process of product information in the centralized procedure" as published on the EMEA website (http://www.emea.europa.eu/ – Human Medicines)

- Application procedures - Product Information Templates - reference documents)
Once the medicinal product is authorised and in all cases BEFORE the medicinal product is placed on the market, specimens of the final outer and immediate packaging and the package leaflet of all product presentations must be submitted to the EMEA within a timeframe agreed between the EMEA and the marketing authorisation holder.

6.3. Accelerated Assessment:

The same principles for the accelerated assessment procedure in accordance with Article 14(9) of Regulation (EC) 726/2004 apply for ATMPs and the "guideline on the Procedure for Accelerated Assessment Pursuant to Article 14 (9) of Regulation (EC) No 726/2004" (http://www.emea.europa.eu/pdfs/human/euleg/41912705en.pdf).

[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.

Where possible, the applicant should submit the request at least 10 working days in advance for consideration at both CAT and CHMP.

7. Withdrawal

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 appeal process, the applicant shall communicate its reasons for doing so to the EMEA.

The EMEA 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). Withdrawal of the application after adoption of the opinion does not prevent that this information is made publicly available.

8. Re-examination

Within 60 calendar days following receipt of the grounds for the request, the CHMP shall re-examine its opinion after consultation of the CAT. The procedure and timetables to be followed are presented in the document "Procedural advice for Re-examination of CHMP opinions (EMEA/CHMP/50745/2005 Rev.1) ".

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 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.

DEFINITIONS

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
EMEA: 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 Oustanding Issues (LoOI)
OE: Oral Explanation
SAG: Scientific Advisory Group
WPs: Working Parties