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Procedural advice on the certification of quality and non-clinical data for small and medium sized enterprises developing advanced therapy medicinal products

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- Update to section 5.2. to allow for electronic submission of the Certification application to EMA and CAT members, in line with current practice.

[I] Following publication of Regulation (EC) No 668/2009

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Procedural advice on the certification of the quality and non-clinical data for small and medium sized enterprises developing advanced therapy medicinal products

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Executive summary

Article 18 of Regulation (EC) No 1394/2007[1] provides that Small and Medium-sized Enterprises (SMEs) developing an Advanced Therapy Medicinal Product (ATMP) may submit to the European Medicines Agency (EMA) all relevant quality and, where available, non-clinical data required in accordance with modules 3 and 4 of Annex I to Directive 2001/83/EC[2] (as amended) on the Community code relating to medicinal products for human use, for scientific evaluation and certification.

Provisions for the evaluation and certification of such data are laid down by the Commission in Regulation (EC) No 668/2009[3].

This document gives guidance and describes the procedures, timelines and practical steps to be followed by the applicants and the EMA for the submission, evaluation of a certification application and if applicable the issuing of the certificate.

1. Introduction (background)

This document is intended to provide guidance to SMEs developing ATMPs (Applicants) on issues associated with the submission, evaluation and certification of quality and non-clinical data by the EMA.

In the foreseeable future, it is expected that with growing experience of the Committee on Advanced Therapies (CAT), there may be a need to update this procedural guidance.

2. Scope

- This procedural advice document concerns the certification of quality and, where available, non-clinical data submitted by SMEs developing ATMPs.

- Only SMEs companies can apply for such type of certificate; therefore the Applicant must have already obtained an SME status as per Commission Recommendation 2003/361/EC4 prior to applying for certification procedure.

- Certification of quality and non-clinical data is only applicable for ATMPs (as defined in Article 2 of Regulation (EC) No 1394/2007).

- This document provides guidance on the procedure, timelines and dossier structure that SMEs should fulfil in order for the EMA to issue when applicable a certificate of quality and where applicable non clinical data.

- The submission to be filed by the SME will be in accordance with Article 2 of Commission Regulation (EC) No 668/2009. The Committee for Advanced Therapies (CAT) is responsible for evaluating applications for certification.

3. Legal basis

The legal basis for the certification of quality and non-clinical data for SMEs are explained in Recital 25 and provided in Article 18 of Regulation (EC) No 1394/2007:

Recital 25

Studies necessary to demonstrate the quality and non-clinical safety of advanced therapy medicinal products are often carried out by small and medium-sized enterprises. As an incentive to conduct those studies, a system of evaluation and certification of the resulting data by the Agency, independently of any marketing authorisation application, should be introduced. Even though the certification would not be legally binding, this system should also aim at facilitating the evaluation of any future application for clinical trials and marketing authorisation application based on the same data.

"Article 18

Certification of quality and non-clinical data

Small and medium-sized enterprises developing an advanced therapy medicinal product may submit to the Agency all relevant quality and, where available, non-clinical data required in accordance with modules 3 and 4 of Annex I to Directive 2001/83/EC, for scientific evaluation and certification.

The Commission shall lay down provisions for the evaluation and certification of such data, in accordance with the regulatory procedure referred to in Article 26(2)."

In addition, Commission Regulation (EC) No 668/2009 lays down the provisions for the evaluation and certification of quality and non-clinical data relating to ATMPs submitted by SMEs to the EMA.

This procedural guidance has to be read in conjunction with the "Scientific guideline on the minimum quality and non-clinical data for certification of advanced therapy medicinal products" (EMEA/ CAT/486831/2008) [5]. Other relevant documents are listed in the "Reference" section.

4. Principles of the certification

Objectives of the certification system

The certification system aims at giving the SMEs an incentive to develop ATMPs.

The certification procedure is a stand-alone evaluation procedure, which is independent from a future application for marketing authorisation. A certificate issued by the EMA is not legally binding with regard to any future regulatory procedure. Any relevant data, even if already certified, should be submitted again for the purpose of any future regulatory procedure. It could, nevertheless, facilitate

the evaluation of any future application for clinical trial authorisation or a marketing authorisation application (MAA), provided that these applications are based on the same data.

Scope of the certification procedure

The aim of the certification system is to facilitate early dialogue between the SMEs and the Regulators and to help SMEs. The certificate could support SMEs who wish to license out their technology or could be used to attract venture capital allowing the SME to further develop their product.

The scope of the certification procedure is to certify that each submitted study complies with the relevant scientific and technical requirements set out in Annex I of Directive 2001/83/EC and adequately follows state-of-the-art scientific standards and guidelines. For these reasons, the evaluation of the data submitted for certification will be conducted taking into account the same scientific and technical requirements applicable to the evaluation of a MAA. It is acknowledged that certification dossiers are likely to contain more limited data: not all sections as defined by part I of Annex I to Directive 2001/83/EC may be completed for the application for certification. Please refer to the scientific guideline on the minimum quality and non clinical data for certification of advanced therapy medicinal products (EMEA/CAT/486831/2008).

The certification procedure addresses only the scientific evaluation of experimental data already generated with the product, i.e., to provide companies a “snapshot” in time of their data with respect to the review standards of an Marketing Authorisation Application (MAA). The certification procedure cannot be used to review products in their conceptual stage or for ‘platform’ technologies. Furthermore, a certificate can not conclude either on the benefit/risk profile of the product.

The certification procedure does not intend to provide advice for further development of the product, since companies should seek such feedback via the scientific advice procedure.

Although the certification procedure is an independent evaluation procedure that will not bind the Agency or National Competent Authorities to any future decision about the product, a certificate could facilitate the evaluation of an application for clinical trial authorisation provided that these applications are based on the same data. A certificate can not conclude on the adequacy of the studies submitted for the product to be used in a clinical trial. The sponsor is still required to submit the clinical trial authorisation application to the National Competent Authorities according to the Clinical trial Directive 2001/20/EC. It is not necessary to get a certificate to apply for Clinical trial authorisation.

Timing of the submission

In accordance with Article 2.1.(b) of Commission Regulation (EC) No 668/2009, an SME can submit an application for a certificate containing either:

- Quality data only

- Quality and Non-Clinical data

When non-clinical studies are submitted for certification, these must be accompanied by quality data on the product tested in the non-clinical studies. An application for the certification can be submitted at any time of the development of an ATMP. However, a minimum quality and where available non-clinical data package will have to be submitted to allow for certification. Interim data from ongoing studies should normally not be submitted for evaluation, unless this information is relevant for the evaluation of other completed studies.

Therefore, the optimum time point to apply for the certification procedure is when the ATMP has reached a level of sufficient development with respect to quality and non-clinical data (please refer to the scientific guideline on the minimum quality and non-clinical data for certification of advanced therapy medicinal products (EMEA/CAT/486831/2008)).

The stage of development will determine the dossier's scientific data content of the certification application: the certification dossier (i.e. data package submitted for certification) is expected to be more comprehensive if a product is in a later stage of development (e.g. already in clinical trial phase). In order to facilitate assessment, the Applicant should provide information about the stage of development and in particular the stage of any study in pre-clinical or clinical setting whether planned, ongoing or completed.

In advance of the certification procedure, the Applicant has the possibility to consult the Innovation Task Force to request an ITF briefing meeting to discuss regulatory, scientific and other issues arising from the development of new therapies and technologies. The ITF arranges briefing meetings to facilitate the informal exchange of information and the provision of guidance early in the development process. Where appropriate, this is done in liaison with Agency scientific committees, working parties and expert groups, and takes into account ongoing international activities.

After you have informed the Agency of your intention to submit a certification application, it is also recommended to request a specific pre-submission meeting (refer to section 5.1.3 Pre-submission meeting).

Content of the certificate

The certificate will refer to the CAT opinion in which a detailed certification evaluation report will identify the quality and, where applicable, non-clinical data submitted and the corresponding testing methodologies followed by the applicant, which have been found acceptable in terms of regulatory compliance and scientific robustness, i.e. meet the scientific and technical requirements set out in section 2.3 and 3 (where applicable 2.4 and 4) of Part I, in Part IV and where relevant to quality (and non-clinical data) in the Introduction and General Principles of Annex I to Directive 2001/83/EC .

Applicants should be aware that the relevance/validity of a certificate will depend on the stage of development of the ATMP as well as on the time point the certificate was issued with respect to further development of the ATMP and overall scientific progress. Applicants should be aware that if a

certificate is granted during early development, the additional data generated during further development will not have been taken into account and the certificate will not represent the full Quality and where applicable non clinical data

5. Evaluation and certification procedure

The activities and timelines for the certification procedure are described below and summarised in Table 1 and Figure 1.

5.1. Pre-submission activities

In accordance with Article 1 of Commission Regulation (EC) No 668/2009, the certification procedure is reserved only for SMEs that are developing an ATMP and are established in the Community. Therefore, the Applicant should have already obtained an SME status as defined by Commission Recommendation 2003/361/EC prior to applying for certification (see EMA SME website[6]).

In addition, if there is any uncertainty whether or not the product falls within the definition of an ATMP, the applicant is strongly encouraged to submit to the EMA a request for scientific recommendation on the classification as ATMP in accordance with Article 17 of Regulation (EC) No 1394/20074). This will allow the applicant to get a confirmation by the CAT that the product is an ATMP. The applicant should be aware that the timetable for this classification procedure is 60 days. Therefore this request should be made sufficiently in advance of the submission for certification and should be finalised prior to the start of the certification procedure. Applicants should refer to the specific procedure for scientific recommendation on ATMP classification[7].

5.1.1. Intention to submit

Applicants should inform the EMA of their intention to submit an application at least 70 days before submission, specifying the intended submission date, the background information relating to the ATMP product and the type of data (quality or quality and non-clinical). Therefore, Applicants should submit information about their ATMP using the appropriate template for the “pre-submission request form” (available on the EMA website which should be addressed to: PA-BUS@ema.europa.eu: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000300.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac058007f4bd),.

The pre-submission request form includes the draft application form and its relevant attachments (), which incorporated the following relevant information:

1) Confirmation of SME status (i.e. EMA-SME number)

2) Background information about the product, indicating that the company already received a classification of their product by the CAT if applicable. If such a scientific recommendation on the classification as ATMP is not available, the applicant should provide a justification of their classification

3) For combined ATMPs (as defined by Regulation EC No 1394/2007) the Applicant should provide information on the status of the medical device or implantable medical device, i.e. declaration that the medical device part of the ATMP meets the essential requirements laid down in Directive 93/42/EEC[8] concerning medical devices and Directive 90/385/EEC[9] on active implantable medical devices.

4) Table of content for Modules 3 and 4 with an indication of the relevant studies/data submitted for certification.

In the pre-submission request form, the Applicant should also provide a statement on the stage of development of the ATMP, i.e. pharmaceutical development, proof of concept studies, toxicology studies and clinical trial application, if relevant.

An overview of the past regulatory procedures conducted with the EMA should also be provided, as appropriate.

The pre-submission request form and supporting documentation should be submitted according to the dates published on the EMA website. EMA will check if the criteria to access the procedure are met (i.e. SME status and ATMP classification).

5.1.2. Eligibility and Appointment of CAT Coordinator

Following the receipt of the pre-submission request form the EMA will check the SME status and classification of the product as ATMP. If case of doubt, the EMA will contact the applicant, seeking clarification and/or suggesting submitting first a request for ATMP classification (see 5.1).

After confirmation of the eligibility to the certification procedure, the CAT will appoint one CAT Coordinator for the certification procedure and CAT (a) peer reviewer(s). An EMA coordinator will also be appointed acting as main contact during the procedure. This will be done 60 days in advance of the start of the certification procedure. The appointments will be notified to the Applicant.

5.1.3. Pre-submission meeting

If the applicant, EMA Coordinator or the CAT Coordinator requires a pre-submission meeting, this may take place approximately 40 to 20 days before the start of the procedure between the Applicant, CAT Coordinator and EMA to address issues with the certification application. Other CAT Members may also participate. If applicants would like to request such meeting, they are advised to contact PA-BUS@ema.europa.eu to request such meeting.

In order to facilitate the discussions and to identify potential issues with the data included in the certification application, the Applicant should provide a detailed outline of the data to be submitted to the CAT and EMA Coordinators at least 10 days before the pre-submission meeting takes place.

A pre-submission meeting (or teleconference) allows Applicants to:

- receive advice to improve the content of the certification application

- identify additional aspects to be included in the certification application,

- obtain further detailed information concerning the certification procedure.

5.2. Submission and validation

Applications for certification should be submitted in accordance with the evaluation timetables published on the EMA website. The draft certification application (dossier) should be submitted to EMA and CAT Coordinators approximately 50 days before the start of the procedure.

Upon submission, the EMA starts a pre-validation of the application, identifies whether additional expertise, involvement of Working Parties or Notified Body (NB) is needed for the evaluation and addresses any issues with the application that may be identified. The EMA coordinator, in conjunction with the CAT-coordinator, will identify the need for a pre-submission meeting if this is not requested by the applicant.

The final certification dossier amended in accordance with recommendations given during the pre-validation and the presubmission meeting, if this took place, should be submitted to the EMA 10 days before the s tart of the evaluation procedure. After validation by the Agency, the final dossier should be sent by the applicant to the CAT Coordinator, the CAT peer reviewer(s) and to all CAT members according to the requirements published on the EMA website.

5.3. Evaluation

Upon positive validation, the procedure starts according to the timetables published on the EMA website. The appointed CAT Coordinator has a maximum of 40 days from the start of the procedure to prepare and distribute the evaluation report to the EMA, the CAT Peer Reviewer(s) and the other CAT members for review. In their reports, the CAT Coordinator should state that no information related to ATMPs developed by other Applicants is included in the evaluation reports. If such information is needed for the evaluation and included in the report, this should be clearly stated and this information should be highlighted. Upon receipt, the EMA coordinator forwards the evaluation report to the Applicant for information.

In the report, the CAT Coordinator should indicate the need for a site visit of any of the premises where the ATMP is being developed in order to complete the evaluation, and clearly indicate the objectives of the site visits or the need of an oral / written clarification by the Applicant.

By Day 50, the CAT Peer Reviewers provide their peer review comments, the other CAT members provide comments on the certification evaluation report and by Day 55 the CAT Coordinator circulates to the EMA and all CAT members the consolidated evaluation report incorporating the relevant peer review and other comments from CAT members. Consultation of relevant Working Party(s) may take place during the evaluation.

At Day 60, the consolidated evaluation report will be considered, and adopted if possible, by the CAT at their plenary meeting. At this stage and if considered appropriate there could be already an opinion adopted by the CAT. If necessary, the CAT may adopt a request of supplementary information together with a response timetable with a clock stop of 30 or 60 days, as requested by the Applicant, to prepare for the oral / written explanation. If applicable, a site visit request is adopted by the Committee at Day 60 of the procedure.

It is recommended that the CAT Coordinator discuss any possible proposals for a Site Visit directly with their GMP inspectorates or GLP monitoring authorities prior to recommendation of the site visit in the Evaluation Report. It is recommended that the CAT Coordinator discuss any possible proposals for a Site Visit directly with their GMP inspectorates or GLP monitoring authorities prior to recommendation of the site visit in the Evaluation Report.

In case of a request for a site visit the procedure is suspended until the site visit report is made available to EMA and CAT. The procedure restarts at an appropriate time point following the circulation of the site visit report (Day 61). In case it is necessary to consult a NB in order to seek information related to the results of its assessment or to seek an opinion on the conformity of the device part with Annex I to Directive 93/42/EEC or Annex I to Directive 90/385/EEC, a NB will be identified in conjunction with the Applicant and the procedure is suspended until the opinion of the NB has been provided to EMA and CAT. The procedure restarts at an appropriate time point following the circulation of the NB opinion.

The Applicant should be aware that only response to the request for supplementary information and no new data or studies will be accepted for evaluation at this stage of the procedure.

The evaluation clock restarts at Day 61 with the oral explanation by the Applicant or when there is no oral explanation, with the written explanation.

If there is **no oral explanation** (written responses only), the CAT Coordinator prepares and circulates by Day 75 an updated consolidated certification evaluation report based on the discussion at the CAT meetings at Day 60 and taking into account the written explanations from the Applicant at CAT members provided comments by Day 85. The EMA coordinator forwards this certification evaluation report to the Applicant for information.

In case of an **oral explanation** at a CAT meeting, the Applicant shall submit written responses to the Request of supplementary information at least 20 days before the scheduled oral explanation. The presentation/list of participants should be provided 7 days in advance of the CAT meeting. The CAT Coordinator prepares and circulates an updated consolidated certification evaluation report 10 days before the oral explanation. Following the oral explanation the CAT Coordinator prepares and circulates an updated consolidated certification evaluation report at D75 for review by CAT members by Day 85. The EMA coordinator forwards this certification evaluation report to the Applicant for information.

The CAT adopts the opinion on the certification application at Day 90 (or Day 60 if appropriate), including the certification evaluation report, detailing the reasons for the conclusions agreed by the

CAT and a List of Issues (LoI) for future consideration by the Applicant in preparing a future regulatory submission.

Depending on whether the opinion is positive or negative, the EMA will issue a certificate or an advisory letter.

Table 1: Activities and timelines for the Certification procedure

Timeline	Action
Day -70	Pre-submission request form (Intent to submit a certification procedure) sent by Applicant (at the latest 10 days before the CAT meeting). EMA checks if SME/ATMP criteria are fulfilled.
Day -60	Appointment of CAT Coordinator, CAT peer reviewers and EMA Coordinator.
Day -50	Submission of draft certification application to EMA and Coordinators for pre-validation.
Day -40 to -20	Pre-submission meeting (teleconference) with EMA Coordinator/(CAT Coordinator).
Day -10	Submission of final application to EMA, for validation.
Day -5	Submission of final application to CAT Coordinator, CAT peer reviewers and CAT members.
Day 0	Clock start (at official CAT start date).
Day 40	Circulation of Coordinator's certification evaluation report to the CAT. Subsequent transmission of this report, by the EMA, to the Applicant.
Day 40-60	Consultation of relevant Working Parties, as appropriate.
Day 50	Peer review comments from CAT Peer Reviewers. Comments by other CAT members.
Day 55	Circulation of Coordinator's consolidated certification evaluation report including relevant CAT members' comments.
Day 60	CAT discussion/recommendation / (possible opinion). Adoption of request for supplementary information (RSI), if necessary (clock stop)* CAT adoption of site visit, if necessary (clock stop)** CAT decision to consult a relevant NB, if necessary (clock-stop)**
Day 60	Clock-stop (if necessary) */**
Day 61	Restart of the clock. Written/Oral*** explanation.
Day 75	Circulation of updated consolidated Coordinators' certification evaluation report to the CAT. Subsequent transmission of this report, by the EMA, to the Applicant.
Day 85	Comments from CAT members.
Day 90	CAT adoption of opinion including the following document: Certification evaluation report including a list of issues.
Day 95	EMA issues the certificate or an advisory letter and forwards the adopted documents to the Applicant.

* A response timetable may be arranged as necessary (30-60 days). The clock will restart at the next or second next CAT meeting (this will be Day 61).
** A response timetable may be arranged as necessary (until the site visit report/ NB opinion is made available to CAT and EMA).
*** The responses to the request of supplementary information should be provided at least 20 days before the scheduled oral explanation. The CAT Coordinator prepares and circulates the updated consolidated Coordinators' certification evaluation report 10 days before the oral explanation. The Applicant provides the presentation 7 days before the CAT meeting to EMA, CAT Coordinators and CAT members.

5.4. Site visit

When considered necessary to complete the evaluation of the submitted certification application, (a) site visit(s) of any of the premises where the ATMP concerned is being developed or non-clinical testing is performed may be requested by the CAT. The scope and specific subject/objective of the site visit will be described in the Day 60 certification evaluation report.

Examples of appropriate occasions to request a site visit could be:

- concerns as to whether the non-clinical studies submitted in the application have been conducted in accordance with GLP, if claimed so
- issues arising during the assessment of manufacturing/quality data that are best resolved through deeper investigation on site
- to verify the veracity of the submitted data

Applicants are advised that there are no official standards laid down in the Community legislative framework governing early pharmaceutical development activities, e.g. in terms of documentation or data traceability and veracity. However, useful principles to follow may be found in the ICH guideline Q10 and in publications of local scientific organisations, for instance:

http://www.bbsrc.ac.uk/publications/policy/good_scientific_practice.pdf
http://www.mpg.de/pdf/rulesScientificPract.pdf
http://www.dfg.de/aktuelles_presse/reden_stellungnahmen/download/self_regulation_98.pdf
http://ori.dhhs.gov/international/activity/documents/CodeofGoodScientificPractice-Spain_000.pdf

Responsibility for Site Visits

In accordance with Article 3 of the implementing Regulation (EC) No 668/2009 the site visits will be performed by inspectors from Member States who hold the appropriate qualifications.

Site visits to investigate the relation to GLP status of non-clinical studies will be performed by inspectors from the GLP Monitoring Authority of the Member State in which the study was carried out. In the case of studies performed in third countries these will be carried out by inspectors of the GLP Monitoring Authority of the Member States of the CAT Coordinator.

Responsibility for site visits relating to Quality/Manufacture is as follows:

- In the case of activities relating to the collection and testing of human tissues and cells, inspectors appointed pursuant to art. 7 of Directive 2004/23/EC in the Member State in which the activity takes place will be mandated. For sites located in a third country the relevant inspectors of the Member State of the Lead Co-ordinator will be assigned.
- In the case of other activities, the GMP inspectorate of the Member State where the site is located will carry out the site visit. For sites located in a third country the GMP inspectorate of the Member State of the Lead Co-ordinator will be appointed.

In some cases it may be appropriate for the CAT to nominate an expert involved in the assessment to accompany the inspectors.

Site visit requests are adopted by the CAT by Day 60 of the procedure and the procedure is suspended (clock stop) until the report of the site visit is made available to EMA and CAT.

5.5. Combined advanced therapy medicinal product

ATMPs may incorporate as an integral part of the product one or more medical devices or active implantable medical devices. In accordance with Article 6 of Regulation (EC) No 1394/2007, those devices should meet the essential requirements laid down in Directive 93/42/EEC concerning medical devices and Directive 90/385/EEC on the approximation of the laws of the Member States relating to active implantable medical devices, respectively, and if available, this information shall be provided in the application. In the case where a NB has evaluated the device part, the result of this assessment shall be included in the dossier by the Applicant**.**

If the Applicant wishes to include in the certification application the sections related to a device component for which the results of the assessment is not available, it may be necessary to consult a relevant NB therefore suspending the certification procedure until an opinion on the conformity of the device part with Annex I to Directive 93/42/EEC or Annex I to Directive 90/385/EEC from a NB is available.

When the applicant does not submit for certification data relevant to the device part, or the assessment by a NB is not provided, the check of conformity of the medical device with the above-mentioned essential requirements will be excluded from the evaluation and from the certificate. In this case, the evaluation report may also conclude that the interaction and compatibility between cells or tissue and the medical device cannot be evaluated.

5.6. Certification

Following the adoption of an opinion including a positive certification evaluation report by the CAT, the EMA will issue a certificate referring to the opinion and its certification evaluation report which identifies that the quality (and where relevant non-clinical) data submitted and the testing methodology followed by the applicant meet the scientific and technical requirements set out in sections 2.3, and 3 (and where applicable 2.4 and 4) of Part I, in Part IV and, where relevant to quality (and non-clinical data), in the Introduction and General Principles of Annex I to Directive 2001/83/EC;

The certificate is composed of the following:

- Certificate

- CAT opinion

- Certification evaluation report which includes the list of issues.

Following the adoption of an opinion including a negative certification evaluation report by the CAT, the EMA will issue a letter advising the applicant that a certificate cannot be granted. The certification evaluation report will be attached to the advisory letter.

Furthermore, a list of issues as regards to the compliance to the above mentioned scientific and technical requirements for future consideration by the Applicant will be included in both positive and negative evaluation reports.

In both cases, the Applicant will be notified, the CHMP and the European Commission will be informed.

EMA will include in its Annual Report a section containing statistical information on the type and number of certification applications submitted.

6. Requirements for application for certification

6.1. Administrative information

The following documentation should be provided in the initial application for certification:

- Cover letter
- Comprehensive table of content
- An pre-submission request form for certification (ATMPs certification which is available on the EMA website (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000300.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac058007f4bd) and the relevant annexes
- List of manufacturing sites and GMP status
- List of laboratories and GLP status, if applicable
- Agreed minutes of pre-submission meeting
- List of any clinical trials (ongoing or finalised) and their status, if applicable
- Investigator's brochure, if available
- Scientific recommendation on classification as ATMP (if available) or a justification of the proposed classification
- For combined ATMPs, results of the assessment by a NB in accordance with Directive 93/42/EEC or Directive 90/385/EEC of the medical device part or active implantable medical device part (if available)
- Previous certification evaluation reports and certificates for the same product, if applicable.
- Previous scientific advice/protocol assistance given for the same medicinal product, if applicable.
- Statement on the stage of development of the ATMP, i.e. pharmaceutical development, proof of concept studies, toxicology studies and clinical trial application, if relevant.
- Information about the Quality Expert (the relevant expert declaration(s) and signatures should be provided)
- Information about the Non-Clinical Expert, (the relevant expert declaration(s) and signatures should be provided), if applicable

These requirements as well as standard timetables and information relevant to fees payable to the EMA are published on the EMA website (please refer to section 5 of the implementing rules: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000020.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580024910).

6.2. Scientific data

In assembling the dossier for application for certification, Applicants should take into account the "Scientific guideline on the minimum quality and non-clinical data for certification of advanced therapy medicinal products" (EMEA/CAT/486831/2008). The data should be presented as per Modules 3 and 4 of Annex I to Directive 2001/83/EC, i.e. format of the Common Technical Document (CTD), and the dossier should contain a quality overall summary and a non-clinical overview (the latter only if applicable) on the data submitted for certification in the same format as Module 2 of the CTD.

Moreover, it is strongly recommended to discuss the suitability of the data package with EMA and the CAT Coordinator during the pre-submission meeting (please refer to section 5.1.3 Pre-submission meeting).

7. Further certification application submitted for the same ATMP

It is possible that SMEs apply for certification more than once.

Where an application for certification has already been submitted for the same ATMP developed by the same Applicant (whether it led to certification or not), a reference to the previous application, its outcome and an explanation of differences with the new application should be presented. The further (subsequent) certification application shall include all data/sections which have already been submitted (and possibly certified), highlighting the sections that have changed or are novel. The Applicant should also provide the previous CAT certification evaluation report.

In addition, an Applicant that has already submitted an application for certification of quality data, may submit a new certification application that contains also non-clinical data. In this case the (updated) quality part should be re-submitted, with a description of what is the added value and differences of the updated quality part in the new application.

The evaluation and certification of the new submission will be carried out as a 90-day procedure, as above (see section 5.3).

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

CTD: Common Technical Document

CHMP: Committee for Medicinal Products for Human Use

CPWP: Cell Based products Working Party

BWP: Biologics Working Party

EMA: European Medicines Agency

EMA Coordinator: Scientific Administrator leading the procedure

EC: European Commission

GDP: Good Distribution Practice

GMP: Good Manufacturing Practice

GTWP: Gene Therapy Working Party

LoI List of Issues. The List of issues is a list of all the “deficiencies” of the Quality development and/or non clinical development which need to be taken into consideration before submitting any future regulatory application.

MAA: Marketing Authorisation Application

NB: Notified Body

PTM: Product Team Member

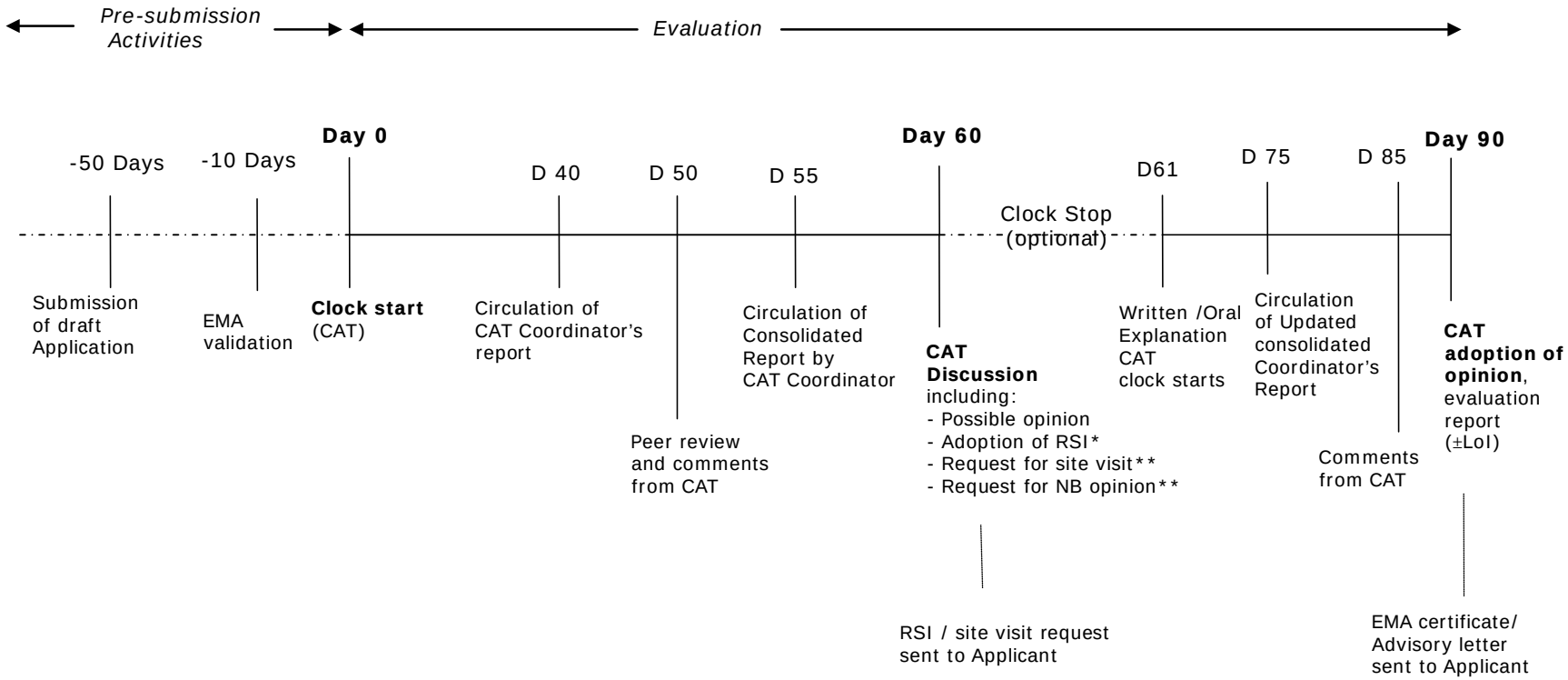
PTM-MQC/CNC: PTM from the ex Inspections Sector

RSI: Request for Supplementary Information

SMEs: Small and Medium-sized Enterprises

WPs: Working Parties

Figure 1 - Timelines for certification of quality and non-clinical data for SMEs developing ATMPs



*The clock stop will be 30 or 60 days

**In case of site visit/consultation of NB clock stop is until site visit report/NB opinion is made available

4 References

[1] 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

[2] Annex I to Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, as amended by Directive 2003/63/EC and Directive 2009/120/EC.

[3] Commission Regulation (EC) No 668/2009 of 24 July 2009 implementing Regulation (EC)No 1394/2007 of the European Parliament and of the Council with regard to the evaluation and certification of quality and non-clinical data relating to advanced therapy medicinal products developed by micro, small and medium-sized enterprises

[4] Commission Recommendation of 6 May 2003 concerning the definition of micro, small and medium-sized enterprises (2003/361/EC)

[5] Scientific guideline on the minimum quality and non-clinical data for certification of advanced therapy medicinal products (EMEA/CAT/486831/2008).

[6] SME webpage: http://www.ema.europa.eu/SME/SMEoverview.htm

[7] Procedural advice on the provision of scientific recommendation on classification of advanced therapy medicinal products in accordance with Article 17 of Regulation (EC) No 1394/2007, (EMEA/99623/2009)

[8] Council Directive 93/42/EEC of 14 June 1993 concerning Medical Devices

[9] Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of Member States relating to Active Implantable Medical Devices