15 October 2010
EMA/CAT/486831/2008/corr
Committee for advanced therapies (CAT)

Guideline on the minimum quality and non-clinical data for certification of advanced therapy medicinal products

Draft Agreed by CPWP, GTWP, BWP	March/April/June 2009
Adoption by Committee for advanced therapies for release for consultation	19 June 2009
Release for consultation[I]	4 August 2010
End of consultation (deadline for comments)	31 October 2009
Adoption by Committee for advanced therapies	15 October 2010
Date for coming into effect	15 October 2010

Keywords	*Small and medium-sized enterprises, Advanced therapy medicinal products, quality data, non-clinical data, minimum requirements, Committee for Advanced Therapies, Certification procedure*

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 74 18 85 45
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Guideline on the minimum quality and non-clinical data for certification of advanced therapy medicinal products

Table of contents

Executive summary

This guideline describes the minimum quality and non-clinical set of data that Small and Medium-sized Enterprises (SMEs)[1] developing Advanced Therapy Medicinal Products (ATMPs) should submit for scientific evaluation when seeking EMA certification of quality, or quality and non-clinical data under Article 18 of Regulation (EC) No 1394/2007[2].

1. Introduction (background)

The certification procedure, as described in Regulation (EC) No 1394/2007 and in the implementing Regulation (EC) No 668/2009[3], is an incentive for SMEs to develop ATMPs. It provides for a scientific evaluation and subsequent certification of quality and, where available, non-clinical data submitted within the scope of the procedure.

From a legal perspective, SME applicants can submit applications for certification of ATMPs at any stage of development. To allow for a meaningful certification, a minimum level of product development will be required prior to the submission of an application. It is not possible to certify a product at a conceptual stage (e.g. certification of platform technologies, novel assays, intermediates such as cell banks only (as defined in ICH 5D[4])) without knowing the intended clinical use of the ATMP and initial manufacturing and testing data. Therefore, the dossier should include a clear description of the active substance [II]/ finished medicinal product[III] that is being developed, as well as description of the intended clinical use / indication and the proposed route of administration.

In the course of the ATMP development the applicant will complete progressively the entire set of quality (Module 3) and the non-clinical (Module 4) data. This data should be available by the time of the submission of the Marketing Authorisation Application (MAA). The data submitted for the certification will be a subset of Module 3 and/or 4 and should be presented in line with Annex I to Directive 2001/83/EC[5], i.e. in the format of the Common Technical Document (EU-CTD)[6]. In this regard a risk analysis and eventual clinical experience, although not part of the certification procedure, should be provided in as in module 2 to be supportive and valuable to define the stage of product development and the intended use of the product.

The certification system aims at giving SMEs an incentive to develop ATMPs and, although it is independent from any application from marketing authorisation, it could facilitate the evaluation of any future application for clinical trial and marketing authorisation based on the same data.

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.

[II] For the purpose of this document the terms *active substance, substance* and *drug substance* are used interchangeably

[III] For the purpose of this document the terms *finished medicinal product* and *drug product* are used interchangeably

2. Scope

This multidisciplinary guideline is intended for SME applicants developing ATMPs.

This guideline addresses the scientific content of an application for certification of quality and non-clinical data, and in particular intends to define the minimum data content for the certification dossier (related to Module 3 and 4, if the latter is applicable).

The extent of information of the certification dossier is expected to be consistent with the stage of development of the ATMP.

This guideline does not provide detailed scientific guidance for the development, manufacturing and quality control as well as non-clinical and clinical development of ATMPs, as these are addressed in specific guidance (see "References" section)[7].

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[2].

Provisions for the evaluation and certification of such data are laid down by the Commission in Regulation (EC) No 668/2009[3] and in particular Article 2 paragraphs 1(e) and (f) define the minimum quality and non-clinical data that must be included in the certification application. Article 5 of the same regulation assigns the task to the EMA of preparing the scientific guidelines relating to the minimum quality and non-clinical data required for the certification of ATMPs.

This guideline should be read in conjunction with the '*Procedural advice on the certification of Quality and Non-clinical data for Small and Medium-sized Enterprises developing Advanced Therapy Medicinal Products*' (EMEA/CAT/418458/2008)[8] and the other documents listed in the "*Reference*" section with particular attention to Annex I to Directive 2001/83/EC[5] and Directive 2004/23/EC[9] and its implementing Directives.

4. Scientific data

4.1. General consideration

All data should be submitted following the relevant headings of the EU-CTD according to Notice to Applicants (NTA), Volume 2B[6].

With regards to quality (Q) *data*, this type of submission should include at least general information and information related to the starting and raw materials, manufacturing process of the active substance(s), data on characterisation of the active substance(s) (limited to the data necessary to

adequately describe the active substance(s)), control of substance(s), and description and composition of the finished medicinal product.

Information on medical device(s) should be provided in module 3.2.R of the CTD (e.g. results of the assessment of the medical device by a notified body) and in relevant Quality sections. Any information on a structural component is expected to be in all relevant Quality sections.

With regards to non-clinical data, this type of submission should include at least primary pharmacodynamic data supporting the rationale for the proposed therapeutic use, pharmacokinetics bio-distribution data, if relevant and at least one toxicity study. It is expected that non-clinical testing is performed for the product that is or has been subject to a Quality certification.

The applicant may have already conducted some non-clinical (NC) pharmacology studies (proof-of-concept studies). When such studies would support the quality data, these data could be included and the results may be summarised in the non-clinical overview. In such case, these non-clinical data will be considered supportive only and will not be part of the formal certification.

A more extensive product development and characterisation is expected to be in place when the applicant is performing Good Laboratories Practice (GLP) safety studies.

If there is already some clinical experience with the ATMP, then a summary of the clinical findings may be included in the application. Although this data will not be part of the certification, it may contribute to understanding the relevance of the non-clinical findings for humans.

Follow-up certification applications (please refer to 'Procedural advice on the certification of Quality and Non-clinical data for Small and Medium-sized Enterprises developing Advanced Therapy Medicinal Products' (EMEA/CAT/418458/2008)

When further developing the manufacturing process, the product development will have evolved to a stage where significant improvement have been achieved, e.g. the reproducibility of the manufacturing process has been addressed, characterisation of the substance/medicinal product has been performed and where interim specification have been set. At such a point, a follow up on Q or Q and NC certification can be submitted.

Any follow-up certification application concerning previously certified Q or Q and NC product is expected to include significant additional data e.g. a new non-clinical safety study or improved quality data. A justification of the significance of the additional information and the detail of the differences compared to the initial application should be provided by the applicant.

In the foreseeable future, it is expected that with growing experience of the Committee on Advanced Therapies (CAT), there will be a need to update the guidelines concerning ATMPs. Therefore, users of this guideline should always check whether a newer guideline has been published which further specifies the issues discussed below.

4.2. Content of Module 2

The SME Applicant should provide an Introduction, a quality overall summary and a non-clinical overview (the latter if applicable) on the data submitted for certification.

In the Introduction (section 2.2) clear description of active substance / medicinal product that is being developed, as well as description of the intended clinical use / indication and the proposed route of administration should be included.

The Quality overall summary and the non-clinical overview should be constructed according to the Notice to Applicants, volume 2B.

A non-clinical overview presenting the non-clinical data to be certified and appropriate additional supportive data in the context of the ongoing development of the ATMP should be provided. Reference is made to the principles described in Annex I to Directive 2001/83/EC although it is understood that only parts of these principles might be applicable depending on the stage of development of the ATMP. Any limitations due to the stage of development should be discussed.

The rationale for the non-clinical development should be discussed and justified, and can be based on the risk analysis further described in Part IV of Annex I to Directive 2001/83/EC.

The outcome of the preliminary analysis using a risk based approach, (in accordance with Annex I to Directive 2001/83/EC) including the methodology followed, should be included in section 2.2 of Module 2, when available. This information will not be formally part of the certification procedure The risk analysis is performed based on existing knowledge of the type of product and its intended use. Especially the risk analysis exercise is of critical importance as it would help the applicant to think through the process since the very beginning and plan in advance the approaches to be taken and studies to be performed during the development of the product. The applicant should also summarise in Module 2 (section 2.2) all relevant clinical experience with the product, if available. This information will not be part of the certification procedure, but will be supportive and valuable to define the stage of product development and the intended use of the product.

4.3. Content of Module 3

The aim of this section is to describe in detail the content of Module 3 for certification applications for cell-based medicinal products (somatic cell therapy medicinal products and tissue engineered products) and gene therapy medicinal products[IV].

For certain ATMPs, the starting material, the substance and the finished product can be closely related or nearly identical. For such products, it is possible that information related e.g. to the manufacture or testing of the finished medicinal product is included in the sections on the active substance(s).

Note:
In the tabulated format below, the second column includes the dossier requirements are applicable to all types of ATMPs. Requirements that are only applicable to Cell-based Medicinal Products (CBMP) or to Gene therapy medicinal products (GTMP) can be found in the third column. Within section 4.3 CTD sections numbering are used and are indicated as 'CTD x.x.x.'

CTD Modules	Common dossier requirements applicable to all ATMPs	Specific dossier requirements applicable either to CBMP or GTMP
3.2.S DRUG SUBSTANCE		
3.2.S.1 General Information		
3.2.S.1.1 Nomenclature	The substance should be given a name, most likely to be a common name given by the applicant.	
3.2.S.1.2 Structure	Summary of the physical and biological characteristics of the substance (origin, phenotype, markers of cells, vector used, transgenes, etc.) including a description of any other materials such as bioactive molecules (growth factors, etc.) and structural components	For GTMP: As schematic representation of the major functional genetic elements that will be transferred. In some cases,

[IV] The main product classes qualifying as GTMPs, apart from genetically modified cells, are: a) naked nucleic acids and non-viral vectors, and b) replicating or replication incompetent viral vectors. For Gene therapy products containing cells, the applicants should also take into account the recommendations given on Cell based medicinal products.

	(scaffolds, medical devices, etc.), when these are an integral part of the substance. The purpose of adding these other materials should be explained. Information on the structural component (e.g. medical device, scaffolds, matrices, etc.) shall be included in CTD section 3.2.R.	this would be applicable for cell therapy.
3.2.S.1.3 General Properties	A list should be provided of biological and where appropriate, the physicochemical and other relevant properties of the substance. Where available, a description of the biological activity (potency) should be included.	For GTMP: For viral vectors information on tropism should be provided.
3.2.S.2 Manufacture		
3.2.S.2.1 Manufacturer(s)	The name(s) and address(es) and responsibilities of all manufacturer(s) and site(s) involved in development, including contractors, and of each proposed production site involved in manufacture and testing should be provided.	
3.2.S.2.2 Description of Manufacturing Process and Process Controls	A summary of the manufacturing process, a flow chart of the entire process starting from the receipt of biological fluid/tissue/organ or from cell banks, including, for each step, the starting materials, intermediates (e.g. intermediate cell batches), and reagents used should be provided. Any process control carried out should be indicated, together with the step where it is performed. Although the process may evolve during the phases of development, it should clearly appear that the process is defined and consistently applied. Matrixes/devices/scaffolds or medical devices can be either used during the manufacturing process or be an integral part of an ATMP. In case where such a product is used or	For GTMP: A cell/seed lot system should be considered and described.

	incorporated during the substance manufacturing process, the flow-chart for the substance should indicate at which step it is added. If it is added to the substance to obtain the medicinal product, refer to the medicinal product manufacturing section. Identification of the raw materials that have been added during the process and, where applicable, a statement on the elimination of these raw materials should be added. The validation of the removal of these raw materials during processing would not be expected. Nevertheless, if Q+NQ certification is sought their impact on the NC results may need to be clarified. Information on the scale of production should be provided. If the batch size of the substance cannot be defined, information on the amount of starting material needed to produce a certain amount of substance has to be provided. When feasible, the number of lots manufactured at the time of the certification application with the process as described should be given.	
3.2.S.2.3 Control of Materials	Materials used in the manufacture of the substance (e.g. raw materials, starting materials, reagents) should be listed and information on the source, quality and control of these materials shall be provided. The specific quality and safety requirements for donation, procurement and testing, laid down in Directives 2004/23/EC and 2006/17/EC[10], and the traceability system as required by Regulation (EC) No 1394/2007 shall be considered as early as possible in the development of an ATMP, This information should therefore be included in the first submission done to the EMA in relation to the development of any ATMP having as starting raw materials substances of human origin. A brief discussion of the impact of the potential variability introduced through the human or animal tissues/cells, especially on the manufacturing process and the product, has to be	For CBMP: please refer to the guideline on Human Cell-based Medicinal Products (EMEA/CHMP/410869/2006) For CBMP: A listing of impurities (e.g. residual bovine serum, feeder cells, other cell populations not for the intended action, dead cells) should be included. When dealing with cell lines of embryonic origin, it should be specified

	provided. The applicant shall describe the quality control of any additional substance, structural components (e.g. scaffolds, matrices, devices, bio-materials, bio-molecules or other components), which are combined with the cells of which they form an integral part. If the component is classified as a medical device, all the information regarding the medical device should be included in CTD Section 3.2.R and high level information should be provided in the relevant sections of Module 3 (e.g. 3.2.S.2.3). In case it is not a medical device, information should be provided in relevant section of Module 3 (e.g. 3.2.S.2.3). The presence of residual impurities including animal-derived raw materials, reagents or starting materials should be discussed in the risk analysis exercise. This analysis shall be supplemented with viral detection and viral inactivation/removal strategies.	whether the cell lines are included in a ethically validated registry such as the European Human Embryonic Stem Cell Registry (hESCreg: http://www.hescreg.eu/). For GTMP: A listing of impurities (e.g. residual bovine serum, packaging cells, residual host or plasmid DNA) should be included. For GTMP**:** Cell and virus seed banks: The establishment of a master cell/virus bank is expected. A brief description on source, history and generation should be given. This includes information about the size of the cell and/or virus bank, as well as information about all raw and staring materials used during establishment. Characterisation and possible specifications should be provided in a tabulated overview. i) Minimal requirements for a cell bank:

		producer cell line identity, cell number and viability, purity, sterility (bacterial and fungal), mycoplasma, adventitious viruses and growth characteristics should be specified. ii) Minimal requirements for a virus seed bank: identity, virus concentration, nucleotide sequence of the functional element in the transferred nucleic acid and its expression should be verified. In addition to those requirements described the genomic/phenotypic characterisation, biological activity, sterility (bacterial and fungal), absence of mycoplasma, adventitious virus and replication competent virus (where the product is replication deficient) should be demonstrated. iii) Minimal requirements for a bacterial cell bank: tests for viability, bacterial strain characterisation, genotyping/phenotyping and verification of the plasmid structure (e.g. by restriction analysis) are required. Tests for adventitious agents and endogenous viruses should be carried out.

3.2.S.2.4 Control of Critical Steps and Intermediates	The critical steps in the manufacture need to be identified and investigated.	
3.2.S.2.5 Process Validation and/or Evaluation	Not applicable as minimum requirement for certification applications.	
3.2.S.2.6 Manufacturing Process Development	It is recognised that this section is of limited applicability for certification. However, any development work done to optimise the production operations should be described.	For CBMP: The process should be justified with regards to the cell population to obtain and the contribution of each step should be explained.
3.2.S.3 Characterisation		
3.2.S.3.1 Elucidation of Structure and other Characteristics	The characterisation studies should be sufficient to allow adequate description of the active substance. It should encompass all the components in the product (e.g. scaffolds, matrices, bio-materials, bio-molecules or other components), if applicable. For purity, tests should be applied to provide information on product and process related impurities including microbial (bacterial and fungal) and adventitious viral safety (see also section 3.2.A.2). These quality attributes constitutes the first set of parameters on which reproducibility and specifications will be progressively elaborated during the development.	For CBMP: the identity testing should include identification of the cellular component (addressing at the minimum the phenotype and relevant markers) and identification of the non-cellular components in the context of their required function in the finished medicinal product. The characterisation for the cellular component should also include viability. The suitability of the cell population in terms of purity should be addressed for the intended use. For GTMP: the identity of the gene of interest and the vector should be determined.

3.2.S.3.2 Impurities	It is acknowledged that characterisation of product related impurities might not be available for products in initial development. The plans to identify and characterise these product related impurities and their impact should be addressed.	For CBMP: at the minimum information should be available of the proportion of unwanted cell types and non-viable cells. Product related impurities of non-cellular origin (e.g. degradation products from structural components) identified and characterisation and their impact on the cellular components should be addressed. Process related impurities such as bioactive molecules or feeder cells should be discussed.
3.2.S.4 Control of Substance:		
3.2.S.4.1 Specification(s)	Formal specifications are not required for certification. However, a set of quality attributes established in characterisation will generate the basis for setting specification at the time of MAA. Any preliminary specification should be provided, if available.	For GTMP: In the case of replication deficient viral vectors, a test to detect replication competent viruses should be included.
3.2.S.4.2 Analytical Procedures	The analytical methods used for the testing of the substance should be described. It is not necessary to provide a detailed description of all the analytical procedure, but the documentation should include principle of the method, reagents, assay controls and test procedures for each of the assay submitted for certification.	
3.2.S.4.3 Validation of Analytical Procedures	At least the suitability or qualification of the analytical methods used should be presented. If available, validation data should be submitted.	

3.2.S.4.4 Batch Analyses	Data on all the products manufactured with the current process should be provided in a tabular format. This should include, where applicable, the batch number, batch size, manufacturing site, manufacturing date, control methods, acceptance criteria and the test results. At least the results from one batch manufactured using the equipment and methodology described in 3.2.S.2.2, produced at any scale, should be provided. Data obtained with previous manufacturing processes could be submitted, if relevant.	
3.2.S.4.5 Justification of Specification(s)	If preliminary specifications are proposed, a brief justification for them should be provided.	
3.2.S.5 Reference Standards or Materials	When a reference standard has been used for any of the assays, characterisation data should be provided. The characterisation of a batch of substance should be initiated to establish a reference standard whenever applicable. International standards should be used, when available, for establishing the in-house reference standard.	
3.2.S.6 Container Closure System	Information on the immediate packaging material used for the substance should be provided.	
3.2.S.7 Stability	If the substance is not immediately processed into the medicinal product, at the minimum the storage conditions and storage period should be justified.	
3.2.P DRUG PRODUCT		
3.2.P.1 Description and Composition of the Medicinal Product	The qualitative and quantitative composition of the finished medicinal product should be stated. Identity, cell number and viability should be provided. If available, the measure of purity and biological activity/potency should also be provided.	

3.2.P.2 Pharmaceutical Development	A short description of formulation development, including justification of any new pharmaceutical form or excipient, should be provided. Where applicable, the applicant should justify the choice of any matrix/scaffold/device or medical device used as an integral part of the medicinal product (see also Section 3.2.R).	
3.2.P.2.3 Manufacturing Process Development	Not applicable as minimum requirement for certification application.	
3.2.P.3 Manufacture		
3.2.P.3.1 Manufacturer(s)	The name(s) and address(es) and responsibilities of all manufacturer(s) and site(s) involved in development, including contractors, and of each proposed production site involved in manufacture and testing should be provided. In case of multiple manufacturers contributing to the manufacture of the medicinal product, their respective responsibilities need to be clearly stated.	
3.2.P.3.2 Batch Formula	Where relevant, an appropriate range of batch sizes may be given.	
3.2.P.3.3 Description of Manufacturing Process and Process Controls	In case the manufacturing process of the active substance and the finished product are similar, information on the manufacturing process should be included in the relevant section for the active substance (i.e. section 3.2.S.2.2) and a cross reference to this section should be made for the finished product. A flow chart of the successive steps, from the storage of the substance up to the final medicinal product indicating the components used for each step and including in-process controls when any, should be provided. In addition, a description of the manufacturing procedure should be included. Where a component such as a matrix/scaffold/device or medical device is added to the substance, this step should be identified.	

	Measures taken to ensure the microbiological quality of the product should be detailed.	
3.2.P.3.4 Controls of Critical Steps and Intermediates	In case of critical steps in the manufacture, their identification and strategies for their control should be briefly summarised.	
3.2.P.3.5 Process Validation and/or Evaluation	Not applicable as minimum requirement for certification applications	
3.2.P.4 Control of Excipients:		
3.2.P.4.1 Specifications	References to the Ph. Eur., the pharmacopoeia of an EU Member State, United States Pharmacopeia (USP) or Japanese Pharmacopeia (JP) should be indicated if applicable.	
3.2.P.4.2 Analytical Procedures	In cases where reference to a pharmacopoeial monograph listed under 3.2.P.4.1 cannot be made, the analytical methods used should be described.	
3.2.P.4.3 Validation of the Analytical Procedures	Not applicable as minimum requirement for certification application.	
3.2.P.4.4 Justification of Specifications	Not applicable as minimum requirement for certification application.	
3.2.P.4.5 Excipients of Animal or Human Origin	See section 3.A.2 APPENDICES	
3.2.P.4.6 Novel	Information on any excipient(s) should be described and, where relevant, the interaction	

Excipients	between the excipient and the cells/tissues should be discussed. Information on structural components used as an integral part of the product shall be documented in section 3.2.R Regional Information.	
3.2.P.5 Control of the Medicinal Product		
3.2.P.5.1 Specifications	Any preliminary specification or quality attribute should be provided, if available.	For GTMP: When replication-deficient viruses are used, a test to detect replication-competent viruses (RCV) has to be in place, if not already performed for the substance.
3.2.P.5.2 Analytical Procedures	If applicable, the analytical methods should be described for all tests included in the preliminary specification.	
3.2.P.5.3 Validation of Analytical Procedures	At least the suitability or qualification of the analytical methods used should be addressed. If available, validation data should be submitted.	
3.2.P.5.4 Batch Analyses	If applicable, the batch number, batch size, manufacturing site, manufacturing date, control methods, acceptance criteria and the test results should be listed.	
3.2.P.5.5 Characterisation of Impurities	Additional impurities observed in the medicinal product, but not covered by section 3.2.S.3.2 Impurities, should be identified.	
3.2.P.5.6 Justification of	If preliminary specifications are proposed, a brief justification for them should be provided.	

Specification(s)		
3.2.P.6 Reference Standards or Materials	The parameters for characterisation of the reference standard should be submitted, where applicable. Section 3.2.S.5 - Reference Standards or Materials - may be referred to, where applicable.	
3.2.P.7 Container Closure System	Information on the immediate (i.e. primary) packaging material should be provided.	
3.2.P.8 Stability	When applicable, the parameters known to be critical for the stability of the medicinal product need to be identified and summarised in a tabular format.	
3.2.A APPENDICES		
3.2.A.1 Facilities and Equipment	A brief description of the facilities and equipment should be provided.	
3.2.A.2 Adventitious Agents Safety Evaluation:	All materials of human or animal origin used in the manufacturing process of both substance and medicinal product (starting materials, excipients and reagents), or other materials coming into contact with substance or medicinal product during the manufacturing process, should be identified and their use at production should be described. At the minimum, a preliminary risk analysis exercise should be conducted. A critical point is the appropriate selection and control of starting materials, excipients and reagents. This exercise shall discuss strategies for adventitious agents testing and virus reduction steps at manufacture (see also section 3.2.S.3.1). When the starting raw materials, excipients or reagents are of human origin, any risk of	

	transmission of diseases derived from derogations of donor exclusion criteria or for any other reasons should be justified and documented. Any risks related to TSE shall be presented in a tabular format and addressed in the risk analysis exercise. Detailed information regarding the other adventitious agents, such as bacteria, mycoplasma, and fungi should be provided in appropriate sections within the application. The measures to minimize microbial contamination by proper sourcing/sampling of the starting material should be addressed in the risk analysis exercise.	
3.2.A.3 Excipients	See section 3.2.P.4.6 Novel Excipients.	
3.2.R Regional Information	This section should include all relevant information on medical devices in combined ATMP. In the case where a Notified Body has evaluated the device part, the result of this assessment shall be included in this section. Information on other structural components, bio-materials, scaffolds or matrices shall also be included in this section (see also Section 3.2.S.2.3).	
3.3 Literature References	This can be included where relevant.	

4.4. Content of Module 4

Non-clinical data submitted in an application for certification should be appropriate to contribute to the proof of concept/principle of the ATMP, and for a preliminary safety evaluation of the ATMP. The extent of data is expected to be in relation to the stage of development. It is expected that non-clinical data are obtained with the product produced and tested as described in Module 3 which take into consideration the minimum requirements for Quality data (see paragraph 4.3). Batch analysis data for batches used in non-clinical studies should be provided.

The required minimal set of non-clinical data for certification is described below:

1. Proof of concept/principle (Primary Pharmacodynamics)

The non-clinical pharmacodynamic "proof of concept/principle" including *in vitro* studies and if feasible, at least one study in a relevant *in vivo* animal model(s) reflecting the intended clinical use.

2. Biodistribution (pharmacokinetics) data are normally essential to support the pharmacodynamics and the safety of ATMP (e.g. engineered stem cells, or genetically modified cells). Relevant data should be included in order to support the assessment of the concomitant NC data. These data could be derived from dedicated biodistribution studies or they could be generated through endpoint integration in other type of studies, e.g. “proof of concept” or toxicity studies. The absence of biodistribution data should be justified.

3. Safety (Toxicology / Safety Pharmacology)

At least one safety study (toxicology and/or safety pharmacology) should be provided. These studies are expected to be of appropriate quality and reliability and to follow relevant guidelines where appropriate. They are not required to be GLP studies but are expected to be conducted in accordance to GLP principles and standards. However, as for any medicinal product development, non-clinical safety studies intended to support clinical trials should be GLP compliant.

In certain scientifically well justified cases, a proof of concept study (e.g. in a model of disease) including relevant safety endpoints can also be considered as toxicology study.

Only final reports will be accepted for certification.

The studies, included in an application for certification, should be presented under the relevant headings of the CTD Module 4.

The distinction between non-clinical study reports submitted for certification or submitted as supportive data, when applicable, should be clearly indicated in the Application form.

Definitions

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

ATMP: Advanced Therapy Medicinal Products

BWP: Biologics Working Party

CAT: Committee for Advanced Therapies

CBMP: Cell based medicinal product

CTD: Common Technical Document

CHMP: Committee for Medicinal Products for Human Use

CPWP: Cell based products Working Party

CTA: Clinical Trial Application

EMA: European Medicines Agency

EC: European Commission

GDP: Good Distribution Practice

GLP: Good Laboratories Practice

GMP: Good Manufacturing Practice

GMP/GDP: Inspectors Working Group

GTWP: Gene Therapy Working Party

GTMP: Gene therapy medicinal products

JP: Japanese Pharmacopeia

MAA: Marketing Authorisation Application

NB: Notified Body

NC: non-clinical

NTA: Notice to Applicants

Q: Quality

SMEs: Small and Medium-sized Enterprises

USP: United States Pharmacopeia

WPs: Working Parties

References

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

[2] 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

[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] ICH Q5D – Note for Guidance on Quality of Biotechnological Products: derivation and characterisation of cell substrates used for production of biotechnological/Biological products (CPMP/ICH/294/95)

[5] 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

[6] Notice to Applicants NTA, Vol. 2B: EU-CTD.
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/b/update_200805/ctd_05-2008.pdf

[10] Useful Webpages:

Advanced Therapy Medicinal Products – EMA webpage:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000294.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800241e0

SME webpage:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000059.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800240cc

Advanced Therapy - Scientific Guideline EMA Webpage:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000298.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800862bd

Scientific Human Guidelines – EMA webpage:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000043.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800240cb

[8] Procedural advice on the certification of Quality and Non-clinical data for Small and Medium-sized Enterprises developing Advanced Therapy Medicinal Products (EMEA/CAT/418458/)

[9] Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells

[9] Commission Directive 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells

[11] Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells