17 September 2010
EMA/CAT/45852/2010
Committee for advanced therapies (CAT)

Overview of comments received on draft scientific guideline on the minimum quality and non-clinical data for certification of advanced therapy medicinal products

Interested party (organisations or individuals) that commented on the draft Guideline as released for consultation

Stakeholder no.	Name of organisation or individual
1	Clinigene EC-FP6 Network of Excellence
2	Voisin consulting
3	Inserm Unit 558 on behalf of EU FP6 Integrated Project RISET
4	Cellectis (Carole Desseaux)
5	Europharm smc
6	Centocor

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1. General comments – overview:

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	As intended, this document should be useful given interrogations that SMEs currently have about the process of ATMP certification. The document is far too long given the fact that it does not contain any new information on module 2, 3 and 4. The guideline could be: (i) much more user friendly, (ii) significantly improved and (iii) shortened as it provides accurate references to documents already in existence, the content of which does not need to be reproduced in full. In particular, the Notice for Applicants EU_ctd_NTA_05-2008 (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/b/update_200805/ctd_05-2008.pdf). We would like to strongly recommend that in case CAT wishes that the content of module 3 appears, it would do so as a table only since this layout would be much more user friendly. Another important line of comments relates to how many times could a company go back to the EMA with updated information? There is mention that the information can be updated as development progresses – see Section 4.1 General Considerations Paragraph 7. However in reality, there are few occasions when this can happen and that is at the time of submitting the CTA for a product when the minimum requirements should be met for the first time. The next time is probably at the end of Phase II and the beginning of Phase III. There are not many other occasions when new data will be available	Whereas the information provided in section 4.3 seems to be identical to the Notice to Applicants requirement, this is not the case. The requirements of Marketing authorisation where discussed and reviewed one by one, and only those relevant for the ATMP certification where included in section 4.3. The layout of Section 4.3 – Content of Module 3 has been reorganised in a table format to be more user friendly. This point is addressed in the Procedural guideline (lines 133- and thereafter). In principle for the time being, there are no limitations on how many times a company could submit a certification procedure.

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	and making a submission anyway will be resource intensive for the Company concerned. Therefore rather than saying that companies can go back anytime – which will not happen in reality – it may be useful for the EMEA to give examples of the optimum time they think these applications could be made. Also we do not want to be wasting the Agencies time by submitting premature or incomplete data. Finally, this document is quoting the event that existing guidelines could be modified by CAT. This, by far, is not an emergency in the users' view. Is it not time to realise that there are far too many guidelines already; that the Mother guideline, Note for Guidance on GT products for example is still valid and accurate since it consolidates every other aspects. The Agency may wish to realise that there are so few specialists able to follow the drafting movement, that the private sector might shrink at the same pace, at least when concerning Gene Therapy and Genetically-modified cells ?	This comment is noted.
2	The draft guideline provides valuable information about the scientific information to be provided as part of the certification procedure. However, due to the heterogeneous stages of development of the concerned products, but also due to the high heterogeneity in the nature of the products, the recommendations may not always be easily applicable. We therefore concur that there is likely to be a need to update this procedural guidance with growing experience.	The guideline will indeed be updated when more experience has been gained (planned for 2011-2012). Accepted. This point is already included; see lines 42-43 of Scientific guideline and lines 38-39 of Procedural guideline.
3	RISET welcomes the opportunity to review this draft on “scientific guideline on the minimum quality and non clinical data for certification	Accepted

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	of advanced therapy medicinal products".	
4	No specific question but a general comment: when required Q and NC data are available, the development should be closed to first in man clinical trial. A lot of topics detailed under CTD format in the certification dossier will have to be recorded in the IMPD. Would it be possible to simplify the CTA dossier (with cross reference for example) after a certification procedure?	Comment: Certification procedure could be useful to prepare the IMPD. However, CTA dossier and IMPD format/content is not under the remit of EMA. Each member states should address this point via their NCAs. This message will be forwarded to the Clinical Trial Facilitation Group (CTFG) for discussion.
5	Europharm is in favor of this interesting initiative and it is particularly interesting for SMEs who don't have yet the necessary facilities, resources and experience to carry through to the clinical development phase any new product. In this way SMEs can develop new advanced therapies until a specific point where it is able to gather the minimal necessary quality and non-clinical data and then submit this to the authorities for evaluation and if the evaluation is positive then the SME gets a Certification which basically testifies that all the research and development that has been done, is in line with current European rules and guidelines and is therefore ready to be carried out for the next stages of development and also the most expensive and resource and time consuming phase: the clinical phases. This certificate obviously gives the SME owner an enormous value for the "work already done" and it is then much easier for that SME to out-license its product to bigger Pharma who will then proceed with the project at ease because it already has the "guarantee" from EMEA that the pre-clinical phase has been performed according to current	We note this comment. The legal basis for certification is only provided for ATMPs that comply with the current definitions. In case of doubt, the applicant should seek a scientific recommendation on classification by the CAT. We will inform the European Commission of your suggestion that SME companies would greatly benefit from incentives like the certification procedure for other innovative products (which are not falling within the definition of an ATMP).

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	standards. Europharms' proposal is to open this measure to more than the previous 4 sub-categories of Advanced Therapy Medicinal Products (ATPM's). Many new products which are currently being developed by SMEs don't fall into the 4 sub-categories of ADVANCED THERAPIES (gene therapy medicinal product, somatic cell therapy medicinal product, tissue engineered product or combined advanced therapy medicinal). On the other hand it is also not clear for some products under which classification do they fit. Let's take the example of bacteriophages: This is a biological type of product that doesn´t clearly fit into any of the 4 categories of the bigger category of ADVANCED THERAPIES. However it is really a very innovative and advanced concept under the bigger classification of biological products and hence our suggestion to the European Commission is that this measure should be open to all biological products developed by SMEs and even to any new pharmaceutical product developed by an SME as our understanding this will clearly boost R&D in Europe and augment competitiveness and entrepreneurship of European SME companies.	

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6	It would be useful to have a description of the key elements involved in certification process. Consideration should be given to providing an introductory section that outlines the elements essential to the evaluation of the information provided (see specific comment #2). A major risk in the development of an ATMP is the process changes required to scale up during clinical development and commercial launch and the ability to show comparability. The description of batch size in CTD 3.2.S.2.2 (lines 197-200) is very important to determine the current scale and to assess the risk in future development. It would be valuable if the guidance requested information that could be used to evaluate the comparability (CPMP/BWP/3207/00/rev1, section 1.4) of batches used in the non-clinical studies to allow the judgement of whether the current comparability strategy supports the planned manufacturing process changes (see specific comment #4) and assess the risk in future development.	The EMA will review the need to develop further guideline (e.g. on comparability). At present reference is made to existing specific guidelines (see lines 115-116 of the scientific guideline). This point could be addressed via scientific advice.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Introduction line 7	6	**Comments:** It would be useful if the introduction could include a list of key evaluation elements during the certification process. **Proposed change (if any):** Attention will be paid during the certification process to the adequacy of comparability strategy and planned manufacturing changes, including analytical methods suitable to support these changes.	It should be noted that the certification procedure is not prospective. It is up to Scientific Advice to discuss and agree on planned changes (e.g. adequacy of comparability strategy) to optimise further development.
Section 4.1 Line 64	1	Comments: this paragraph already addresses non-clinical data (module 4) Proposed change (if any): the heading "with regards to non-clinical data should be removed from line 69 to line 64; in fact, it would even read better to change the order of the two paragraphs in whole. One would more easily understand that part of the NC data can be used to substantiate the quality part as well.	Accepted.
Section 4.2	1	Comments: this section is re-iterating several times the same issues, part of which have already been mentioned in Section 4.1 Proposed change (if any): edit in order to consolidate, clarify and shorten	Section 4.1 is an introductory section to the scientific guideline where all the key elements are summarised. Repetition is considered useful for a better understanding.
Section 4.2 line 55	3	**Comments:** The expression “Notice to Applicants” should be written entirely and explicitly before using the	Accepted

		abbreviation. It should also be mentioned in the list of definitions page 14. **Proposed change (if any):** " according to THE NOTICE TO APPLICANTS (NTA)"	
Section 4.2 line 74	3	**Comments:** The expression "Good Laboratory Practice" should be written entirely and explicitly before using the abbreviation. It should also be mentioned in the list of definitions page 14. **Proposed change (if any):** "performing GOOD LABORATORY PRACTICE (GLP) safety studies"	Accepted
Section 4.2 line 98	3	**Comments:** The website link should be added. A part called "What's new" in the "advanced therapy" section of the EMEA's website should be added to facilitate the access to new guidelines and other new information regarding ATMP.	Your comment is noted.
Section 4.2 line 123	2	Comments: The section and format in which the existing clinical data to be submitted, if any, should be clarified. Proposed change (if any): The applicant should also summarise in Module 2 all relevant clinical experience with the product, if available. Clinical experience should preferably be presented according to CTD rules in a dedicated section 2.5 Clinical Overview, but it may also be included in section 2.2 or 2.4 depending on the relevance and the amount of details provided.	Comment: Only high level clinical information should be provided, as it is not in the scope of this procedure to certify also clinical data. Clinical data/information should be included by the applicant in *Module 2.2 CTD Introduction* of the certification application (see section 4.2. Content of Module 2).
Section 4.3	1	Comments: this is just horrible, not new and not user	The content of certification application is not the same as required for a full MAA. Each section of the CTD has been

		friendly Proposed change (if any): suggestion to condense whole section under of a table form since cross-indexation to the genuine reference document: "Notice for Applicants EU_ctd_NTA_05-2008" has been carefully & accurately taken care of.	reviewed to describe the minimum data set that is required for certification. Section 4.3 has been reorganised in a table where CTD modules are listed together with the requirements applicable to ATMPs.
Section 4.3 line 128	3	**Comments:** the detailed description concerns minimum quality data content for certification applications. **Proposed change (if any):** " to describe in detail THE MINIMUM REQUIREMENTS ON the quality data content for certification applications"	Line 148: "quality data" has been removed an replaced by Module 3.
Section 4.3 line 153	2	Comments: The examples of physical and biological characteristics appear specific of cell based product and not gene therapy products. Proposed change (if any): Summary of the physical and biological characteristics of the substance (origin, phenotype, markers of cells, vector used, gene to be transferred, etc.).	Accepted
Section 4.3 line 167	2	Comments: This section is missing info specific for GTMP. Proposed change (if any): Where available, a description of the biological activity should be included. For viral vectors information on tropism should be provided.	This is acceptable.

Section 4.3 line 212	2	Comments: If it often easier to provide the core of the information related to the structural components (scaffold, matrices, devices, bio-materials) in section 3.2.R. Cross- reference to this section should be made, each time it is needed. Proposed change (if any): ~~"…The applicant shall describe the quality control of any additional substance (scaffold, matrices, devices, bio-materials, bio-molecules or other components), which are combined with the cells of which they form an integral part.~~ Information on quality control of the structural components (scaffold, matrices, devices, bio-materials, bio-molecules or other components), which are combined with the cells of which they form an integral part may be included in CTD Section 3.2.R. when judged appropriate.	Line 81-83: the following sentence is added: "If the component is classified as a medical device, all the information regarding the structural component 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)."
Section 4.3 line 217	2	Comments: Minor wording change. Proposed change (if any): "…other cell populations not intended for the ~~intended~~ <u>targeted</u> action, dead cells)…".	The sentence has been reworded as follows: "…other cell population not for the intended action, dead cells).."
Section 4.3 line 217	3	**Comments:** When dealing with cell lines of embryonic origin, it should be specified whether the cell line is part of the European Human Embryonic Stem Cell Registry (hESCreg: http://www.hescreg.eu/). **Proposed change (if any):** "WHEN DEALING WITH	This has been accepted with some changes.

		CELL LINES OF EMBRYONIC ORIGIN, IT SHOULD BE SPECIFIED WHETHER THE CELL LINE IS PART OF THE EUROPEAN HUMAN EMBRYONIC STEM CELL REGISTRY (hESCreg).	
Section 4.3 line 246	3	**Comments:** An error occurred. **Proposed change (if any):** " TESTS for viability"	Accepted.
Section 4.3 line 257	6	**Comments:** Recommend that for an ATMP with a Drug substance the CTD section 3.2.S.2.6 Manufacturing Process Development be utilized to describe changes that will be needed with further development. If the ATMP only has a drug product that CTD section 3.2.P.2.1 or 3.2.P.2.3 is used. **Proposed change (if any):** It is recognized that this section is of limited applicability for certification. However, development work done to optimize the production operations and planned changes to optimize further development should be described.	As minimum requirement for certification, the CTD section on Manufacturing Process Development should be completed only for the DS. An ATMPs could not have only a drug product without a drug substance. If the DP is very similar to the DS, then 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. It should be noted that the certification procedure is not prospective: it is up to Scientific Advice to discuss and agree on planned changes to optimise further development
Section 4.3 line 268	2	Comments: Statement on finished product characterization should be less stringent. Proposed Change (if any): The characterization studies should be sufficient to allow adequate description of the active substance. It should encompass all the components present in the	Accepted. The sentence has been reworded and clarified.

		finished product as far as possible in accordance with state of art.	
Section 4.3 line 269	2	Comments: All the information related to the adventitious agents should preferably be presented in one single section, CTD 3.2.A.2., and cross-reference to this section should be made, each time it is needed. Alternatively, the proposed statement in this section may be deleted in this section and incorporated in section 3.2.A.2. Proposed Change (if any): "…For purity, tests should be applied to provide information on product and process related impurities. Microbial (bacterial and fungal) and adventitious agents' viral safety should be covered in section 3.2.A.2. ~~including microbial (bacterial and fungal) and adventitious viral safety.~~"	Accepted. High level information on microbial (bacterial and fungal) and adventitious agents should remain in this section. Reference to section 3.2.A has been included in the text.
Section 4.3 line 274	2	Comments: Minor wording change Proposed change (if any): "…in the context of their required function in the ~~finished product~~ finished medicinal product…"	Accepted
Section 4.3 line 307	2	Comments: At this stage of development, it is likely that the analytical procedures will still evolve. In addition, providing the test procedure as currently stated is equivalent to providing a detailed description of the	Accepted. The sentence has been reworded.

		procedure which is indicated as unnecessary at that stage. We reworded to make the requirement less stringent. Proposed Changed (if any): "…But the documentation should include the principle of the method, reagents and assay controls to allow for a clear understanding of the assay used and how it is controlled. ~~and test procedure~~ …"	
Section 4.3 line 349	2	Comments: Tests related to the control of the medicinal products should be discussed in Section 3.2.P.5. Proposed Change (if any): "~~*FOR GTMP: When replication-deficient viruses are used, a test to detect replication-competent virus (RCV) has to be in place, if not already performed for the substance*~~"	Accepted
Section 4.3 line 391	3	**Comments:** The expressions referring to "USP" and "JP" should be written entirely and explicitly before using the abbreviations. It should also be mentioned in the list of definitions page 14.	Accepted
Section 4.3 line 405	3	**Comments:** An error occurred. The title of the section it is referred to should also be specified. **Proposed change (if any):** " See section 3.2.A. " APPENDICES", p. 12"	Accepted
Section 4.3 line 411	3	**Comments:** The title of the section it is referred to should be specified.	Accepted

		Proposed change (if any): " Section 3.2.R. "REGIONAL INFORMATION", p. 12"	
Section 4.3 line 416	2	Comments: If a list of preliminary specification is not available, then it could be replaced by a list of quality attributes Proposed Change (if any): "Any preliminary specification or quality attribute should be provided, if available"	Not accepted. Quality attribute is not a standard terminology used in Guidelines and Directives.
Section 4.3 line 416	2	Comments: Tests related to the control of the medicinal products should be discussed in CTD Section 3.2.P.5. and thus the sentence that is currently in line 349 should be moved after line 416. Proposed Change (if any): Add: "*FOR GTMP: When replication-deficient viruses are used, a test to detect replication-competent virus (RCV) has to be in place, if not already performed for the substance*"	Accepted
Section 4.3 line 431	3	**Comments:** The title of the section it is referred to should be specified. **Proposed change (if any):** "section 3.2.S.3.2 "IMPURITIES", p. 8"	Accepted
Section 4.3 line 444	3	**Comments:** The meaning of the word "immediate" is not very clear.	Accepted. The immediate packaging is the primary packaging material.
Section 4.3 line 449	2	Comments: For certain ATMP, the final medicinal product is	Accepted.

		administered to the patient as soon as its manufacture has been completed (e.g. GTMP), in this case stability studies are not applicable Proposed Change (if any): "The plan for stability studies should be presented, or justification should be provided when judged not applicable	The following sentence has been deleted: "The plan for stability studies should be presented."
Section 4.3 line 466	2	Comments: For gene therapy products, the assessment of absence of replication competent viruses needs to be specified as part of viral safety as well. Proposed Change (if any): "…at manufacture (e.g. for certain viral vectors designed to be replication incompetent, the absence of replication competent viruses is to be tested as part of viral safety).	Accepted. This comment on GTMP is to be highlighted in section 3.2.S.3.1 and not in section 3.2.A.2
Section 4.3 line 478	3	**Comments:** The title of the section it is referred to should be specified. **Proposed change (if any):** "See section 3.2.P.4.6. " NOVEL EXCIPIENTS", p. 11"	Accepted
Section 4.4 Line 491	6	**Comments:** There is an error in section numbering under Scientific Data – there are two sections 4.3. **Proposed change (if any):** Change number proceeding Content of Module 4 from 4.3 to 4.4 in the table of contents and in the body of the document.	Accepted
Section 4.4 Line 491	6	**Comments:** Module 4 should request that all lots used in non-clinical studies be tabulated with characterisation	The sentence has been rewarded and clarified. Batch analysis data for batches used in non-clinical studies should be

		results, and in the case of tissue-derived products, donor information, so that comparability can be assessed and a risk assessment performed. If there are insufficient lots available at this stage of development to perform this assessment then it should be justified. **Proposed change (if any):** After the description of the minimal set of non-clinical data required for certification (after line 523), add a request for the data specified above.	provided.
Definitions	3	**Comments:** The definitions of Q, NC, NTA, GLP, USP and JP should be added.	Accepted
References	6	**Comments:** It is suggested to also include a reference to 2006/17/EC *and* 2006/86/EC.	Accepted