17 September 2010
EMA/CAT/45460/2010
Committee for advanced therapies (CAT)

Overview of comments received on procedural advice on the certification of quality and non-clinical data for small and medium-sized enterprises developing 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	Voisin Consulting
2	Inserm Unit 558 on behalf of EU-FP6 integrated Project RISET
3	Cellectis (Carole Desseaux)
4	Tristem Ireland Limited

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1. General comments – overview:

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	We understand the difficulties in setting-up the ATMP Certification Procedure, in part due to the heterogeneous stages of development of the concerned products, but also due to the high heterogeneity in the nature of the products. We therefore concur that there is likely to be a need to update this procedural guidance with growing experience. Lines 71, 72 and 73 state: "*The scope of the evaluation is to certify that* ***each submitted study complies*** *with the relevant scientific and technical requirement set out in the Annex I to Directive 2001/83/EC and adequately follows state-of-the-art scientific standards and guidelines*". The development of an ATMP is often highly supported by academic research and associated publications. Based on this literature, the range of non clinical studies to be conducted on the product itself may be greatly reduced. We assume that the literature available will be taken into account when assessing the level of compliance of the product with the requirements set out in annex I to Directive 2001/83/EC, taking into account its stage of development. This may need to be clarified in the procedural guidance.	Noted. For the development of ATMPs, the risk based approach can be applied to determine the studies to be performed. This Risk based approach can be based, also, on available literature data. (Please see also the ICH guideline Q8) Note that the statement in lines now 98-99 is to clarify that each study will be looked at separately: the certification procedure will make no statements on the completeness or appropriateness of the module 3 or module 4 (entire sections)
2	RISET welcomes the opportunity to review this draft on "Procedural advice on the certification of quality and non-clinical data for small and medium-sized enterprises developing advanced therapy medicinal products".	The table and figure 1 outline the most frequently expected scenarios.

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	The optional steps of the procedure could be indicated in Figure 1 with dotted lines and in Table 1.	
4	Such advice/certification will be very welcome to SMEs which generally have limited, if any, regulatory experience. Particularly in the field of ATMPs where both scientists and regulators are pushing the boundaries of current knowledge and regulation. The timeline is very long for what is likely to be a small volume of data: a minimum of 7 months from start to finish (Table 1). As many if not all SMEs are poorly funded, this is a long period of cash burn waiting for an outcome which, in all likelihood, would be used by the providers of funding to decide whether to invest further. Can the time be accelerated? Otherwise the objective of incentivising SMEs to develop ATMPs may be compromised. Will there be any fee for this certification procedure? There is no mention one way or the other in the Consultation Document.	The timelines are fixed in legislation (maximum 90 days). For small data packages, they seem long, but for larger packages (ie if the product has already entered into clinical trials), the packages can be substantial. However, please note that the time of the pre-submission activities have been reduced. Yes, but it is only 10 % of the fee indicated in the fee explanatory note on fees payable to the European Medicines Agency (38 100 euros for quality data only and 57200 euros for quality and non clinical data).

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 5	1	Comments: "*accordance with modules 3 and 4 of Annex I to Directive 2001/83/EC[2] (as amended) on the*" We recommend to move the superscript to annex I[2] and indicate as part of reference 2 the texts that are forming annex I, e.g. directive 2003/63/EC and directive 2009/120/EC, as this may not always be obvious to SMEs. Proposed change (if any): "*accordance with modules 3 and 4 of Annex I[2] to Directive 2001/83/EC (as amended) on the*"	Accepted.
Line 74	1	Comments: We suggest removing the sentence of lines 74 and 75 as the first paragraph of the section provides more accurate and sufficient information. Proposed change (if any): ~~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.~~	Not accepted. This sentence provides more explanation.
Line 89-90	3	Is the reverse true ie if the data are not certified, this	This had now been clarified in line 121.

		automatically implies that the product cannot be used in clinical trial ?	
Line 102-103	2	**Comments:** It should be made a reference to "Scientific Guideline on the minimum quality and non-clinical data for certification of advanced therapy medicinal products".	This has been added in lines 105-106.
Line 114-115	1	Comments: "*In any case, it is strongly recommended that in advance of the submission for certification, the Applicant consults the EMEA and appointed CAT Coordinators about the appropriateness of the data included in the submission (refer to section 5.2.3 Pre-submission meeting).*" Numbering of Pre-submission Section is not correct. We recommend being more precise regarding the process for setting-up such a meeting (see comments below) Proposed change (if any): "*In any case, it is strongly recommended that in advance of the submission for certification, the Applicant consults the EMEA and appointed CAT Coordinators about the appropriateness of the data included in the submission (refer to section 5.1.4 Pre-submission meeting).*"	This has now been clarified in line 228. Request should be submitted to V-PD-BUS: PA-BUS@ema.europa.eu
Line 127	1	Comments: "*Applicants should be aware that if a certificate is granted during early development its relevance/validity is likely to be limited*."	A sentence has been added in line 109-110: The certification procedure cannot be used to review products in their conceptual stage or for 'platform' technologies.

		We recommend the EMEA to be more specific, or at least provide a recommendation as to the state of quality development that is at least awaited e.g. critical quality attributes should already be defined with associated analytical procedures, etc. In addition, "is likely to be limited" is vague. It would be helpful to clarify what the EMEA means by this. Alternatively, if it appears too difficult to define, reference could be made to Article 2 of Commission Regulation (EC) No 668/2009 with regard to the minimal requirements to be included in an application. Proposed change (if any): Not Applicable	Also, the applicant can only submit a certification procedure when it complies with the Scientific guideline on the minimum quality and non clinical data for certification. Reference has been added in lines 105-106. This has been clarified.
Line 141-143	1	Comments: The EMEA offers the Applicant the opportunity to request a pre-submission meeting. It is not clear however how the meeting request is initiated. We recommend adding information on this point. Proposed change (if any): "*Applicants should inform the EMEA of their intention to submit an application and to request a pre-submission meeting (refer to Section 5.1.4) at least 4 months 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).*"	This has been clarified in section 5.1.3.
Line 147-148	1	Comments: "*Background information about the product, including*	

		the Applicant's proposal and justification on the classification of their product as ATMP (i.e. gene therapy medicinal product, somatic cell therapy medicinal product, tissue engineered product or combined advanced therapy medicinal product)." This "background information" seems to duplicate the objective of the ATMP classification. Proposed change (if any): *"Background information about the product, including the Applicant's proposal and justification on the classification of their product as ATMP (i.e. gene therapy medicinal product, somatic cell therapy medicinal product, tissue engineered product or combined advanced therapy medicinal product").* *Add: "In case of doubts regarding the classification of the product,* ***the Applicant is strongly encouraged to submit to the EMEA a request for the scientific recommendation on the classification as ATMP in accordance with Article 17 of Regulation (EC) No 1394/2007 (refer to Section 5.1.2)."***	The following sentence has been added in lines 174-181: 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[i].
Line 147-148	1	Comments: "*In the letter of intent, 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 or list of the past regulatory procedures conducted with the EMEA may be helpful, e.g. orphan	

		status, ATMP classification, ATMP certification, paediatric investigation plan, scientific advice /protocol assistance procedures… Proposed change (if any): "*In the letter of intent, 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 EMEA should also be provided, as appropriate".**	This has been taken into account in lines 197-198.
Line 147-150	3	It should be possible to refer to the previous EMEA letter about classification	Accepted.
Line 176	1	Comments: "*This request should be made sufficiently in advance of the submission for certification and should be ☐inalized prior to the start of the certification procedure. Applicants should refer to the specific procedure for scientific recommendation on Advanced Therapy (AT) classification*." We suggest keeping the same abbreviation for designating advanced therapies. Proposed change (if any): "*This request should be made sufficiently in advance of the submission for certification and should be ☐inalized prior to the start of the certification procedure. Applicants should refer to the specific procedure for*	This has been updated.

		scientific recommendation on Advanced Therapy ***Medicinal Product (ATMP)*** *classification*."	
Line 185	3	**Presubmission meeting:** Please specify who takes the initiative of this meeting, EMEA or applicant or both.	This has been clarified in section 5.1.3.
Line 188	2	**Comments:** If such pre-submission meeting is organised, at least one of the CAT Coordinators should participate Proposed change (if any): "ONE OF THE CAT Coordinators SHOULD also participate."	The CAT Coordinator will be invited to the pre-submission meeting. Please refer to line 225.
Line 196	2	**Proposed change (if any): "**IDENTIFIES"	This has been updated.
Line 197	2	**Proposed change (if any):** "ADDRESSES"	This has been updated.
Line 198	1	Comments: We recommend clarifying the difference between "pre-submission meeting" and "validation teleconference" as the objectives seem similar. **Proposed change (if any):** Not Applicable	There will only be a pre-submission meeting, the validation TC has been removed. Please refer to section 5.1.3.
Line 198-200	2	**Comments:** Who is requiring?	This can be the EMA, applicant or the CAT Coordinator.
Line 205-206	2	**Comments:** This sentence appears unclear. Are 30 to 20 days in addition to the 1 month provided in Figure 1 or are they included? If they are included, the expression "extended	Extended validation will not happen any more. There will be only 10 days for the validation. The content of the certification procedure will be discussed at the pre-submission meeting.

		validation" is not justified. If they are in addition, it should be clearly indicated L 198 or L 200.	
Line 208-209	1	**Comments:** The format of the submission (electronic (email, CD-ROM, portal), paper) should be specified as well as the need for providing original documents. We believe that considering the trend towards electronic submissions, a CD-ROM or DVD with all the support documentation should suffice **Proposed change (if any):** Not Applicable	This has been clarified. Electronic submission is acceptable. CD should be provided to the EMA. Dossier requirements will be provided in the validation letter which will be received by the applicant.
Line 208-209	2	**Proposed change (if any):** "The final dossier should be sent BY THE APPLICANT to the EMEA…"	Accepted
Line 226-228	3	The visit is a good idea for applicant to benefit from EMA experience and to identify non-compliant process early in the development. However, it is not sure that this procedure is really considered as an incentive if there is not more indications about the visit follow up. Is this visit of facilities a proposition or obligation for getting certification? Can the applicant refuse the visit? If so, is the certification procedure automatically stopped? What is the "status" of this visit? It is said later that inspectors will perform the visit but at last is this visit considered as an inspection? will later certification request be submitted to documentation of corrective actions? Thank you for clarifying.	The site visit will be agreed and requested at the CAT. The applicant has to provide a written consent to the site visit request. A rejection of the site visit by the applicant (or the site concerend) does not per se constitute an automatic termination of the certification procedure. The CAT will have to come to a conclusion without the site visit report. A site visit will not be considered an inspection. However, the applicants could voluntarily ask the inspectors to carry out, in parallel, an inspection. This would make sense if the stage of development and the state of the concerned facilities comply with GMP or GLP standards. It is foreseen that the concerned site will be given time to comment on the observations of the inspectors prior to

			submission of a final site visit report to the CAT. As this is a new territory for the inspectors, a learning process and changes to the site visit procedure (EMA SOP/INS/2001, currently a draft) are likely.
Line 242-246	1	**Comments:** "*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 EMEA and CAT. The procedure restarts at an appropriate time point following the circulation of the NB opinion."* It is previously mentioned that the need for consulting a notified body (NB) is identified at the time of the validation (line 197). It does not seem appropriate to create a clock stop without further time control/limitation. We believe that the consultation of a notified body should not extend the duration of the procedure, or that the extension is set to a maximum of a month. This time extension is indeed penalizing the applicant compared to standard applications. Indeed, article 9 of regulation (EC) No 1394/2007 states that "*the notified body shall transmit the information within a period of one month"*. Proposed change (if any): Not Applicable	This comment is taken into consideration.

Line 268-286	2	**Comments:** In reference to Article 3 of 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 (Official Journal L 194, 25/7/2009 p. 7 - 10)), it seems the applicant can refuse site visit. The consequences of such refusal should be indicated	It is clarified that the applicant can refuse a site visit. The consequence to the certification procedure will be decided upon by the CAT on a case by case basis.
Line 303-304	2	**Comments:** It should be clarified if it is an expert who has been involved in a previous assessment and which one? If it is an expert who will be involved in the site visit, clarify if this expertise is only during the site visit or more widely covering the assessment process.	This has been clarified in the procedure. If necessary an expert can accompany the Inspector.
Line 341-342	2	**Comments:** Annual Report should also give an overview of previous years for follow-up.	Accepted.
Line 381	2	**Comments:** If multiple applications are done, this would be included in the statistical information in the Annual Report (referred to L 341).	Yes, that is correct.

[i] 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)