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30 May 2024

European Medicines Agency
Committee for Advanced Therapies (CAT)

RE: EMA/CAT/123573/2024
Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials

Dear Sir or Madam:

PDA appreciates the opportunity to provide feedback to the EMA as the agency develops and establishes best practices for the efficient prioritization, development, issuance, and use of guidance documents. In our attached comments, PDA offers specific comments and feedback that we believe will be helpful in the further development of this program.

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, device manufacturing, and quality. Our comments have been prepared by a committee of PDA members with expertise in advanced therapy medicinal product manufacturing and quality considerations on behalf of PDA's Advanced Therapy Medicinal Products Advisory Board.

If you have any questions, please do not hesitate to contact me via email at wright@pda.org.

Sincerely,

Glenn Wright
President and CEO

Cc: Josh Eaton, PDA

30 May 2024

Submission of comments on Guideline on quality, non-clinical and clinical requirements 4 for investigational advanced therapy medicinal products 5 in clinical trials (EMA/CAT/123573/2024)

Comments from:

Parenteral Drug Association

A team of Parenteral Drug Association (PDA) members convened to provide a response to the comment solicitation. The comments submitted to the EMA are provided below for reference and as a record of PDA's ongoing commitment to promote regulatory convergence as well as provide information to PDA's members and the pharmaceutical manufacturing community.

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by a committee of experts representing our Advanced Therapy Medicinal Products (ATMP) Advisory Board and Board of Directors.

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	In general, the Parenteral Drug Association (PDA) welcomes this draft guideline to support the development and management of investigational ATMPs through clinical phase (exploratory and confirmatory) and to provide consistency in the information provided within the IMPD for these novel products. We acknowledge the use of a science and risk-based strategies to the development of the manufacturing process as product knowledge and process understanding are increased. The guideline should note consistently and clearly throughout the document where the application of a phase-appropriate approach for the purposes of the development and management of the investigational ATMP may be acceptable. In S.4.3, "Validation of analytical procedures" the validation of analytical procedures is identified as "an evolving process" through the lifecycle, however in S.2.3 "Control of Materials" there is not clear guidance that a phase-appropriate approach may be acceptable for the qualification of the raw materials used in the process (there is only guidance on the assurance of the qualification from the safety perspective prior to human clinical trials). In these instances, a phase-appropriate approach can be applied using a science and risk-based approach, while still identifying those activities that must be performed prior to a stage (e.g., those that may impact patient safety).	
	PDA notes that the glossary that has been added based on comment from the first consultation identifies the names of the acronyms used and can be even more useful to the reader if it also provided the definition / explanation of the term (consistent with other EMA guideline documents, e.g. EudraLex Volume 4 "Guidelines on Good Manufacturing Practice Specific to Advanced Therapy Medicinal Products".	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
345-346		Comment: PDA recommends clarification on the estimation of the overall culture duration including definition of the term "procurement" as it relates to the collection of the cellular starting material is needed, and specifically when the "clock" starts for procurement in order to determine the overall culture duration. In addition, during early development (at the time of exploratory clinical trials) the growth characteristics of the cellular materials may not be well understood especially for the patient populations to be manufactured, and thus setting an acceptable maximum or range for the number of population doublings is difficult and may be unnecessarily restrictive criterion for manufacturing. Proposed change (if any): "For cell-based products, the overall culture duration should be indicated in days after procurement (collection) of the cellular starting material." "An estimation of the population doublings should be established during development, as additional process knowledge is gained."	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
417 – 418		Comment: PDA sees a need for raw materials to be qualified from the perspective of safety prior to human clinical trials, as appropriate. A risk-based approach should be used where the level of qualification required for the raw material (for use in the manufacture of the investigational ATMP) should be commensurate with the criticality of the material (as it relates to product quality attributes). Proposed change (if any): "The qualification of the materials used in the manufacture of the ATMP should be commensurate with the risk as used in the in the manufacturing process. The level of qualification of the raw material should be commensurate with the criticality of the material (as it relates to product quality attributes). Prior to human clinical trials, qualification should focus on the safety of the raw materials."	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
624-626		Comment: PDA notes that the complete absence of bacterial and fungal contamination cannot be determined given the limitations (*i.e.,* the limit of sensitivity) of the tests/assays and the text would benefit by reflecting this. This is consistent with ICH Q5A terminology and aligns with Ph. Eur. Proposed change (if any): "The presence of bacterial and fungal contamination..." or "The absence of detectable bacterial or fungal contamination..."	
766-768		Comment: PDA recommends removing "vectors" in parentheses for the critical starting material, as this recommendation may also relate to other types of critical starting materials used in the manufacture of an investigational ATMP. Note that the other materials in this list do not have accompanying examples provided within parentheses. Proposed change (if any): "Of note it is highly recommended to keep retain samples of critical starting materials, intermediates, active substance and finished product, when possible, in the event that comparability studies are required during future product development or after licensure."	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
1514		Comment: PDA recognizes the response provided for section A.1 as part of the first consultation to the lack of content within this section. Additional guidance on the instances in which this will be addressed by GMP inspections is greatly appreciated. For example, this can be interpreted to mean that an inspection of the facility (those listed in S.2.1 and P.3.1) for EU facility aspects is required prior to the production of drug substance / drug product in order to support a FIH trial. Proposed change (if any): "Information regarding the facilities and equipment used for the manufacture of the drug substance and drug product in accordance with ICH M4Q should be provided."	

Please add more rows if needed.