EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

01 October 2018

Submission of comments on ' Good Clinical Practice for Advanced Therapy Medicinal Products' (TSC 01/2018)

Comments from:

Name of organisation or individual
European Confederation of Pharmaceutical Entrepreneurs – EUCOPE

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	EUCOPE welcomes the consultation on the Good Clinical Practice for Advanced Therapy Medicinal Products (ATMPs). The advances in ATMPs brings the promise not simply of treatment to manage the symptoms of a diverse group of severe, disabling or life-limiting conditions but the promise of one-time disease modifying treatments that can transform and save lives. EUCOPE members recognise the importance of regulatory requirements for the research, development and manufacturing of these products as measures of quality control and welcome the opportunity to comment below. EUCOPE's comments aim to help ensure the Good Clinical Practice for Advanced Therapy Medicinal Products will support research and development in this field and avoid unintentionally creating overly restrictive requirements for research programmes that could stifle research.	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*

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)*
Footnote No.3 page 3		Comment: correction of typographical error Proposed change (if any): Regulation (EU) No 536/2014 on clinical trials of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use and repealing Directive 2001/20/EC, 2014 OJ L158/1.	
Footnote page 3 and other pages		Comment: the references to the Official Journals are inconsistently presented across all footnotes in the document. Example from page 3, footnote No.1: Proposed change (if any): 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 (2007, OJ L324/121)	
69		Comment: correction of wording Proposed change (if any): ATMPs (delete)	
70		Comment: correction of wording	

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		Proposed change (if any): conduct of clinical trials (…)	
80		Comment: correction of wording Proposed change (if any): that contain cells or tissues of human origin, follow up of (…)	
91-94 and 106-110		Comment: these two bullet points partially repeat the same concept. Proposed change (if any): • The relationship of the anticipated benefits to the risks of the ATMP should be at least as favourable as existing alternative approaches • For populations that might ultimately be amenable to organ transplantation or transplantation of haematopoetic stem cells, sponsors should consider whether exposure to the ATMP would cause sensitization, prevent the subject from accessing future therapies, and potentially compromise future transplant success (*e.g.* immunogenicity in case of gene therapy). […]	

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		(delete)	
95		Comment: clarification of the wording Proposed change (if any): When the clinical trial population involve paediatric subjects or foetuses	
84-136		Comment: In the clinical trial design section, additional clarifications on the distinction between the definitions of "data lock" versus the "data snapshot" language would be welcome on the expectations from the sponsors in the context of early phases trials for rare diseases or cell therapies in oncology. Proposed change (if any):	
100-101		Comment: additional relevant example Proposed change (if any): (*e.g.* severe genetic diseases, rare diseases)	
103-105		Comment: The request for data from the adult population might delay the initiation of potential life-saving therapies especially for children and poses a significant disadvantage for this patient group. This applies to indications, for instance ALL, which are prevalent both in adults and	

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		paediatric patients. The development of life-saving therapies should not be delayed for the paediatric patient population. The request to generate data in the adult population first should be applicable only to indication/treatment line, in which an alternative curative treatment exist but not for life-threatening disease without curative therapeutic options. Proposed change (if any): "Prior studies in adults should have been performed if feasible for the condition in question unless life-threatening, or else a rationale should explain why these are unethical, not feasible or not relevant (e.g. in cases of diseases exclusively affecting paediatric patients)."	
105		Comment: formatting correction Proposed change (if any): (*e.g.* in cases of diseases exclusively affecting paediatric patients)	
115-117		Comment: clarification of the wording Proposed change (if any): Whilst comparison to standard of care or no treatment sometimes makes double-blinding infeasible for investigators/for the surgical investigator team, blinding for subjects should be employed wherever	

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		possible.	
121-122		Comment: clarification of the wording Proposed change (if any): The risk posed by the procedure should be duly explained in the study protocol.	
130		Comment: introduction of a recommended good practice for autologous investigational products: back-up cells before the subject is treated. Proposed change (if any): In the case of autologous investigational ATMPs based on the use of $CD34^+$ haematopoietic stem cells, a sample of unmodified $CD34^+$ cells should be collected and appropriately stored before administration of any conditioning regime or of the investigational product. This back-up sample should consist of a number of cells sufficient to reconstitute the subject's bone marrow in case of engraftment failure.	
135-136		Comment: clarification of the wording Proposed change (if any): The sponsor should select a cohort size which is both feasible and adequate to meet study objectives.	

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144		Comment: clarification of the wording Proposed change (if any): the confirmation that a traceability system is in place, that enables (…)	
165-166		Comment: additional relevant example Proposed change (if any): Therefore, it is acknowledged that in the case of some ATMPs it may not be possible to perform formal dose finding studies. It is also acknowledged that, in the case of autologous investigational ATMPs, the final dose of the product will be dependent on the biological make-up of each subject.	
167-172		Comment: Many of those processes are part of routine clinical practice, i.e. leukapheresis. It is not recommended to explain in further detail in the protocol as this is not done for similar routine interventions like blood draws, lumbar punctures or tumor biopsies. To ensure quality requirements would be best placed in a separate document. Proposed change (if any): "Upstream interventions on subjects: In an autologous setting, the subject must undergo a medical intervention to extract cells/tissues prior	

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		to the manufacture and administration of the product. The process of taking biopsies/extracting cells may entail risks to the subject and may also have an impact on the quality and safety of the product. Therefore, it is important that such processes are clearly explained in case they deviate from routine clinical practice. The level of documentation should be adapted to the complexity and the novelty of the procedure (delete)."	
171		Comment: correction of typographical error Proposed change (if any): important that such processes are clearly explained. The level of documentation (…)	
182-186		Comment: The exact process for release of out-of-specification (OOS) product is complex and will differ by country/region for global trials. It is therefore recommended to not describe this process in the clinical trial protocol but to refer to the company standard operating procedure implemented for this situation. Proposed change (if any): Risk-minimization measures: Where appropriate, information should be provided on the measures that should be put in place to protect clinical trial subjects from identified risks. For example, if the results of the sterility test of the product are not available at release,	

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		appropriate mitigation measures should be implemented, including liaison with clinical staff if deemed necessary, especially where out of specification test results are obtained after the release of the product. The details of this process can be described in a separate document.	
193-196		Comment: clarification of the wording and correction of typographical errors Proposed change (if any): If the ATMP has the potential for prolonged biological activity after a single administration, the long-term follow-up of subjects should be considered. The follow-up strategy should be based on a risk-assessment taking into consideration all information available to the sponsor. envisaged. The follow-up strategy should be based (…)	
199-200		Comment: additional relevant example and clarification of wording Proposed change (if any): The follow up for subjects treated should be implemented also in cases of early termination of the clinical trials, or post treatment withdrawal of subjects from a clinical trial.	
204		Comment: addition of a missing word	

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		Proposed change (if any): information on whether the medical device part(s) comply (…)	
209		Comment: addition of a missing word Proposed change (if any): Annex 1 of the Medical Device Regulation 2017/745 (…)	
217		Comment: formatting corrections Proposed change (if any): appropriate and relevant *in vivo* and *in vitro* models.	
220		Comment: clarification of the wording Proposed change (if any): In some cases, testing the investigational product in animals may (…)	
222-223		Comment: clarification of the wording Proposed change (if any): does not permit to predict the safety profile of the actual investigational product. It follows that the ability of (…)	

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248		Comment: correction of typographical error Proposed change (if any): instructions are laid down in a separate document available at the site (*e.g.* handling instructions)	
257		Comment: correction of typographical error Proposed change (if any): document available at the site (*e.g.* handling instructions)	
265-271		Comment: Same comment as above (lines 182-186). The exact process for release of out-of-specification (OOS) product is complex and will differ by country/region for global trials. It is therefore recommended to not describe this process in the investigator`s brochure but to refer to the company standard operating procedure implemented for this situation or a stand-alone document. The same applies to how to contact the clinical trial subject if a health concern is identified. Proposed change (if any): Safety of the clinical trial subject: information on short and long term safety issues particular to ATMPs such as infections, immunogenicity/immunosuppression and malignant	

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		transformation should be provided. (delete)	
273-274		Comment: clarification of the wording Proposed change (if any): The level of information should be commensurate to the risks.	
291		Comment: clarification of the wording: trial documentation must always be recorded contemporaneously in the TMF/ISF Proposed change (if any): In case of investigational ATMPs with short shelf life, timelines should be clearly documented contemporaneously in the trial records in relation to time from manufacture to time of subject administration to enable verification of the quality of the product.	
Footnote No.8 page 9		Comment: it would be beneficial not to state web addresses in guideline documents, it is suggested to state the full name of the guidelines used as reference instead Proposed change (if any): Guidelines of 22 November 2017, Good Manufacturing Practice for Advanced Therapy Medicinal Products, C(2017)7694	

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299-300		Comment: clarification of the wording Proposed change (if any): When the administration requires specific concomitant therapy and/or involves surgical procedures that could have an impact on subject safety or the efficacy of the product (…)	
305-306		Comment: correction of the wording Proposed change (if any): If the presence of the sponsor is envisaged before the start of the clinical trial, this should be explained in the informed consent.	
312-313		Comment: clarification of the wording Proposed change (if any): The individual product should be traceable from delivery to the clinical site up to the administration to the clinical trial subject.	
318-320		Comment: clarification of the wording Proposed change (if any): The traceability system should be bidirectional (from donor to subject and from subject to donor) and data should be kept for 30 years after the expiry date of the product, or longer if required by the clinical	

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		trial authorisation.	
332		Comment: addition of missing text Proposed change (if any): The requirements for traceability are without prejudice to the provision Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation).	
363-364		Comment: stating the duration and nature of the long-term follow-up study should not be required as this could change depending on discussions with the CHMP on a case by case basis. It is recognised the clinical trial protocol should state the planned availability of a long-term follow-up study. Proposed change (if any): The availability of a planned follow-up (*e.g.* interventional study, non interventional study, registry) should be described in the clinical trial protocol.	
367		Comment: correction of typographical error	

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		Proposed change (if any): Where applicable, it should be clearly specified which follow-up activities should take place prior (…)	
378-383		Comment: this paragraph leads to confusion in between the clinical trials and the long-term follow-up studies. Amendments are suggested to clarify that only the follow-up studies are described here. Proposed change (if any): Detailed arrangements for the remote conduct of follow-up activities should be explained in the long-term protocol or an associated document. In accordance with applicable local requirements, the sponsor should ensure that approval of a protocol is obtained in the country where the long-term follow-up takes place. (delete)	
385-386		Comment: clarification of the wording Proposed change (if any): If a subject stops participation in the trial or does not want to continue administration of the investigational product (repeated dosing) (…)	
390		Comment: correction of typographical error	

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		Proposed change (if any): The sponsor should ensure that there is a process in place for follow-up of the subjects treated (…)	
392-393		Comment: the national competent authorities should be contacted if a sponsor was to cease trading activities. Suggested wording is proposed to this effect. Proposed change (if any): (…) for instance, by providing appropriate information to the healthcare establishments involved in the clinical trial and to the relevant national competent authorities.	
399		Comment: addition of wording Proposed change (if any): Alert cards should contain as minimum the name of the subject, the name and address of the original treatment site, an investigator contact number (…)	
401-413		Comment: Regulatory convergent guidance on the administration of out of specification products is needed. Specifically, we recommend harmonization with Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products, adopted by the	

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		European Commission on 22 November 2017. Proposed change (if any): The exact process for release of out-of-specification (OOS) product is complex and will differ by country/region for global trials. It is therefore recommended to not describe this process in the clinical trial protocol but to refer to the company standard operating procedure implemented for this situation.	
409-413		Comment: We are of the general opinion that the confirmation of acceptance of the product by the investigator should be submitted as a notification of breach of predefined specifications which has been assessed and requested by an investigator rather than an Urgent Safety Measure as the plausibility of a safety issue should preclude the release of the out-of-specifications product. Proposed change (if any): When the request of the investigator is received, the sponsor should provide him/her with its evaluation of the risks and notify him/her that the out of specification product is being supplied at his/her request. The confirmation of the investigator to accept the product should be recorded by the sponsor and the relevant competent authority should be notified of such events (as breach of predefined specifications).	
417		Comment: formatting correction	

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		Proposed change (if any): (*e.g.* the cell-based part and medical device part in the case of combined ATMPs)	
430-431		Comment: formatting correction Proposed change (if any): adverse events possibly related to mandatory concomitant medication (*e.g.* immunosuppression).	
432		Comment: the safety training is not limited to the investigator, it is also applicable to the clinical site study team. The proposed amendment reflects this. Proposed change (if any): The sponsor should provide information and training to the investigator and the site study team on any additional protocol and/or product specific requirements for the reporting of adverse events.	
434-436		Comment: correction of typographical error Proposed change (if any): In cases where long-term follow-up of trial subjects is foreseen, aspects related to the reporting of adverse events during the follow-up period should be clearly specified as part of the long-term follow-	

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		up arrangements.	
440		Comment: addition of missing text Proposed change (if any): Article 48 of the Regulation (EC) No 536/2014 (…)	

Please add more rows if needed.