<November 10th, 2015>

Leem comments on Commission proposal for Good Manufacturing Practice for Advanced Therapy Medicinal Products

1. General comments

Line number(s) of the relevant text (e.g. Lines 20-23)	General comment (if any)
	GMP for ATMP should be a document annexed to standard GMP (a new Annex) and not a stand-alone document. The following suggestions are for consideration to be included in this GMP document: 1) Link with regulation and/or guidance for human tissue and cell (in particular, DIRECTIVES 2004/23/EC, 2006/17/EC, 2006/86/EC)); 2) Link with regulation and/or guidance for GMO products (in particular, DIRECTIVE 2001/18/CE); **3)** Link with regulation and/ or guidance for biological safety (non-viral and viral adventitious agents) for starting materials and raw materials and excipients of biological origin (in particular, EP 5.2.12 Raw materials for the production of cell-based and gene therapy medicinal products, Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products EMA/410/01)**.** It would be good to generate additional specific Chapters on the following points to consider: 1) Specific requirements for primary packaging for frozen products at ultra-low temperature

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	2) Specific requirements for CCIT (container closure integrity) for frozen products 3) Specific requirements for labelling of investigational and commercial ATMPs: i.e. glossary for abbreviations, requirements for label/ink compatibility with storage and transport at ultra-low temperature. 4) Requirements for non-pharmacopoeia excipients (i.e., novel excipients), excipients of biological origin (quality, safety). 5) Differentiate GMP requirements between i.e. pre-clinical ATMPs, first-in-man investigational ATMPs and commercial ATMPs 6) Propose guidance on development and validation process of tissue and cell based products. 7) Propose guidance for pooling of materials of different donors

2. Specific comments on text

Line number(s) of the relevant text	Comment and rationale; proposed changes
Q1	Those principles are sufficient annexed to standard GMP for medicinal product. GMP for ATMP should be a document in addition to standard GMP and not a stand-alone document. It has to be considered as a new annex of GMP like annex 2 to annex 7 or annex 14. Risk based approach should be considered in this chapter.
Q2	No
Q3	Good Manufacturing Practices for "product preparation" is following the Directive 2004/23 as published for example in France in October 2010 for preparation. If the product is classified as ATMP, this present annex should apply.
Q4	Additional specificity: as the definition of the ATMP relies on the nature of the cells, this definition can vary in function of the manipulation variation. To ensure continuous product consistency, the training file of operators shall be supported by documented dry-runs before to perform GMP lots. Quality Assurance Unit may be mentioned as in revisited GMP chapter 2.
Q5	4.2.1 is not necessary as more appropriate description is given in the recent chapter 5 of GMP.

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Q6	The flexibility is given by introducing QRM in the chapter 5 of GMP; as ATMPs don't have any sterilization step the premises should be aseptic during the all process and additional flexibility has to be considered cautiously in regard to part III Q9.
Q7	In order to insure flexibility on the process definition, we need to first minimize first the risk related with environment and premises; sterility rules may refer to annexe 1 and chapter 5 without further flexibility as annex 1 relies on more than 30 years of experience on sterility outcomes.
Q8	Grade C should apply only for documented closed system or for manufacturing step before sterilization if any. Grade C cannot be the immediate environment of the grade A if there is no sterilization step (like cell therapy products). Flexibility cannot be in regard to sterility. Moreover if the product is manufactured in grade A with C background, this product cannot be acceptable for FDA then Europe will not be able to export product and will lose dynamic attractiveness; the GMP rules need to stay at the same level. Line 162: source material should be added.
Q9	The equipment should be documented periodically regarding its aseptic use. Primary container should be tested for integrity. The strategy of testing can rely on validation data based on mock runs if the method is destructive and/or products are rare.
Q10	Electronic system should be validated according to annex 11. It is welcome that this chapter mentions the possibility to perform some changes during on-going clinical trials especially for earlier stage. The PSF which is the key element of current annex 13 is not mentioned here. The list of requested document can be included in a unique document called the product specification file according to annex 13

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	of GMP in revision. We welcome the notion of unit reconciliation which is not clear in annex 13. The certification template should be provided or referenced as in annex 13.
Q11 and Q12	The notion of continuous validation process can be further described as there is nothing about this paradigm in annex 13 and annex 15 is out-of-scope of the investigational product. It will be very relevant to be specific to ATMP.
Q13	Line 448 may be changed as "Only starting and raw materials" which have been released by the person/department responsible for QC should be used. We welcome that authorized tissue establishment do not require additional audit. There is a lack of chapter about manufacturer analytical identification & assay for raw and starting material. It will be very useful to mitigate these assays with initial material risk assessment and scoring which may evolve during the development. Add a chapter on the testing necessary to evaluate the variability due to change in raw and starting material lot. This will be embedded by the change control strategy. Line 487 : add chemical inactivation
Q14 Lines 541 -543	For i.e. as a stock of primary feeder cells can be limited, the possibility to manufacture a stock issued from a new donor can be given based on comparability exercise results. As primary cells are in limited quantity compared to lineage, it should be easily switched from one to another donor.
Q15 Line 561	Include a section on labelling placed directly after filling of primary container (very small size) and labelling after packaging into the secondary packaging material

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Q15 Line 573	In earlier development, the definition of substantial modification is not an easy approach as the quality attributes are not totally determined and test methods are not totally validated. Provide a non-exhaustive list for substantial and non-substantial changes in each type of ATMPs.
Q15 Line 649	Cleaning validation may document the action of residual cleaning agents on microbiological risk, GMO diffusion risk and cell toxicity risk. During first-in-human studies, cleaning validation can be still ongoing if supported by cumulated cleaning data generated during qualification phases. The cleaning validation report could be provided later.
	Secondary packaging materials (e.g., to protect from light, humidity, to prevent from temperature excursions) are also of importance. ….The suitability of primary **and secondary** packaging materials…
Q16 Lines 708-727	Validation strategy of IMP should be determined by the manufacturer on a case-by-case basis and a risk-based approach should be taken. Aspects to be taken into account are: number of recipients by lot, variability of starting material, the clinical application (e.g., for orphan indications, only a few batches may be manufactured during the clinical development), full-process validation may be a post-approval commitment based on the complexity of the manufacturing process (e.g., number cell/tissue manipulations) etc...
Q17 Line 716	The effort of validation for these products should consider autologous or allogeneic application and the type of release. …. Add a sentence: **Full process validation should be performed prior to the submission of the**

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	MAA according to annex 15, unless otherwise agreed upon with the competent authorities
Q18 Lines 773-774	Please refer to Eudralex Volume 4, Annex 16 for a comprehensive overview of the QP responsibilities
Line 748	Product Specification File is missing
Line 850	The release is under the responsibility of the sponsor of clinical trial according to annex 13.
Line 757 “ For ATMPs, it may be justified to rely on testing performed in the third country, *e.g.* in case of autologous products, as the limited quantities of material available may impede double release testing.”	We agree, in case of limitation in product availability, EU recognition may be possible on a third country release; this recognition should be supported by anticipated releaser qualification.
Q19 Line 976-978 “- Replacement of routine batch testing by process validation.	**This sentence is totally inconsistent with current annex 13**.

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While process validation is usually not required for investigational medicinal products, it may be very important when routine in-process or release testing is limited or not possible."	
Q19 Lines 982-986 "A continuous assessment of the effectiveness of the quality assurance system is important. Results of parameters identified as quality attribute or as critical should be trended and checked to make sure that they are consistent with each other. Any calculations should be critically examined. No trending is however required in connection with an investigational ATMP."	Please refer to the ICH terms: Critical Quality Attribute (CQA) and critical process parameter (CPP).
Q19 Lines 1000-1007 section 12.4	After the marketing authorisation and during clinical development, stability studies should be performed. Provide guidance on stability studies during clinical development.

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Q20	Qualification of Supplier/Product is necessary before using the product in human.
Q21 Lines 1057-1060, Section 15	Refer to European GMO guidance Indicate that the manufacturer has the obligations of country specific GMO regulation.
Q22	We fully agree and who should verify that the user (hospital, pharmacy) are trained to perform these tasks adequately? The manufacturer or sponsor? Stability data on reconstituted product should be a key element of stability study.
Q23	We agree that reconstitution is outside GMP, the ATMP's reconstitution should be considered as another injectable medicine product reconstitution.
Q24	Reconstitution can be : Thawing, fluid transfer, diluting, Washing is not reconstitution but it is a manufacturing step.
Q25	These specific operations should be performed by Pharmacy or under the responsibility of pharmacist