September 23, 2016

Unit B5 – "Medicinal products – policy, authorisation and monitoring"
European Commission
DM24 02/133
B-1049 Brussels, Belgium

via email to SANTE-B5-ADVANCED-THERAPIES@ec.europa.eu

Dear Sir or Madam:

ISPE (International Society for Pharmaceutical Engineering) would like to submit comments on the draft Guidelines on Good Manufacturing Practice for Advanced Therapy Medicinal Products. The following pages contain both general and specifc comments on the document.

ISPE is an individual membership Society of more than 18,000 professionals involved in the manufacture of pharmaceuticals and related products. All scientific and technical areas of the pharmaceutical manufacturing industry are represented among the ISPE Membership. We appreciate the opportunity to submit these comments for your consideration.

Sincerely,

Theodora Kourti, PhD
Senior Vice President for Global Regulatory Affairs, ISPE

EC Consultation Document, Good Manufacturing Practice for Advanced Therapy Medicinal Products

http://ec.europa.eu/health/human-use/advanced-therapies/developments/index_en.htm

Comments submitted by: **ISPE (International Society for Pharmaceutical Engineering)**
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General Comments

ISPE welcomes the opportunity to input into the Commission's development of GMPs for ATMPs. Society members understand the rationale for a stand-alone guidance but would ask for an explanation of the special needs (i.e. goals) that ATMPs require from a GMP perspective to serve as a clarification and facilitate understanding. ISPE has concerns that there are opportunities missed to build upon the extensive expertise and knowledge contained within the EU GMPs. The current document is a combination of requirements and in a lot of cases a literal copy of the GMPs already established in Volume 4, Annex 1 and Annex 2. There are a small number of EudraLex references (e.g., site master files, Annex 12), so other referrals must be possible and we propose that cross referencing would be much preferred in order to ensure alignment is maintained.

If this document is to remain independent of Volume 4, the guideline may need to be extended to cover key concepts- For example "so called pharmaceutical quality system" is introduced in the introduction but is not formally defined. Further concerns arise when later in the document there is a reference to an immature quality system and a weak quality system, again with no definitions.

Another key concept with no definition or reference is the Risk Based Approach (RBA) introduced in Chapter 2. As a stand-alone document, it should formally develop the concept. The RBA is suggested as the approach to allow the flexibility that the development and manufacture of ATMPs require. However, Chapter 2.2 suggests that the RBA has limitations and can be inadequate, giving examples, proposing the manufacturer needs to put in place additional measures, and later strongly encouraging that the advice of the competent authorities is sought. By questioning the RBA adequacy, the chapter transmits an ambiguous message.

Further ambiguity arises through the structure and content of section 4.2.2. Aseptic Environment. The document appears to mix-up aseptic environments with all grades of clean classified areas, with expected minimum requirements (e.g. class C for preparation of solutions, etc.) and accepted practices (e.g. different background grade for a grade A area, etc.). In that respect is a grade D an aseptic environment or what is the definition of aseptic environment? In another instance, the maximum number of non-viable particulate is established twice (lines 530 and 560) one as maximum permitted values and in the other as recommended action limits.

The guide establishes the requirements of sterile medicinal product's conditions for the production of ATMPs for clean room classification, gowning practices, etc. This implies that all ATMPs are sterile products and eliminates the possibility to implement alternative solutions, like closed systems in controlled but not classified areas based on a risk based approach.

Chapter 9.4 focuses on prevention of cross-contamination in production and summarises a list of measures that can be considered. However, there is not a section dedicated to multi-product production at the same facility. It is under section 9.5 Aseptic manufacturing where a few examples are given. Multi-product production is key in the manufacturing of ATMPs. For instance, is a patient specific batch regarded as a single product? Or just a different batch? The clarification of the regulatory perspective in this regard would be of great value.

Process validation of ATMPs is developed under section 10.3 in Chapter 10 (Qualification and Validation). It is also discussed in section 9.5.3 Aseptic processing validation in Chapter 9 (Production). The first considers the important limitations of ATMP's processes whereas the second describes expectations that are very similar, if not the same, to the fill and finish operations of a (larger volume) sterile medicinal product. It is recommended that the topic be discussed in just one place to reduce confusion.

Overall, ISPE recommends consideration to be given to improving the structure and clarity in the guideline. The challenges of achieving this are not under-estimated, especially when recognising that ATMPs embrace such a wide family of products/process that have to be covered in a single standalone GMP guideline. An ongoing challenge will also be the maintenance of the guideline. Greater reliance on EudraLex may assist here.

Finally, Volume 4 Annex 2 of EU guidelines for GMP is understood to cover ATMPs. In the same way Annex 1 is relevant for all ATMPs that need to fulfil the requirements of sterile medicinal products. ISPE recommends a clear implementation path be developed in order to avoid confusion and conflict over what GMPs are applicable. The implementation plan should consider the future development of Annex 1 and 2. We suggest all stakeholders will need to understand whether Annex 2 will again be reviewed to exclude ATMPs and whether the new Annex 1 under review will be applicable to ATMPs. Without such clarification, ambiguity for both manufacturers and inspectorates may well ensue.

Specific Comments on the Text

Line Number	Current Text	Proposed Change	Rationale or Comment
112	there is an adequate documentation system that ensures that appropriate specifications are laid down….that the production process is clearly understood….	Product realisation is achieved by designing, planning, implementing, maintaining and continuously improving a system that allows the consistent delivery of products with appropriate quality attributes;	No documentation system can ensure that appropriate specifications are 'laid down'. The term "laid down" is in itself inappropriate and would be better replaced by "developed". Moreover, a documentation system itself does not create process understanding.
118	and the identification of any process deviation as well as the implementation of appropriate corrective action(s)	state of control is established and maintained by developing and using effective monitoring and control systems for process performance and product quality.	It is not the role of a manufacturing process to enable identification of process deviations. Nor should the manufacturing process define corrective actions. These needs form part of the overall quality system.
176-177	…the manufacturer is responsible to put in place additional measures	the sentence is not required	The risk based approach should define the appropriate measures to put in place. No additional measures should be required.
244	…the active substance	Delete 'active substance'	ATMPs are defined as medicinal products for human use.
226-340	Examples of the application of the risk-based approach	Delete examples	Examples in a guide often become expectations that are implemented even if they can be shown not to be relevant. Even if examples are for clarification, they should

Line Number	Current Text	Proposed Change	Rationale or Comment
			not be part of a general guideline document, but could be an Annex.
241	Finally, it needs to be assessed if the control strategy (*i.e.* qualification of suppliers) is sufficient to eliminate the risks or to mitigate them to an acceptable level.	Finally, it needs to be assessed if the control strategy (*i.e.* qualification of suppliers) is sufficient to mitigate the risks to an acceptable level.	It is not possible to eliminate risk.
293-302	It is stressed that it is the responsibility of the manufacturer to ensure that the manufacturing of ATMPs is done under aseptic conditions,	Revise text to allow other conditions as appropriate.	The expectation is overly restrictive in that the manufacturing of all ATMPs should be done under aseptic conditions and establishes a minimum requirement independent of any risk analysis.
694	The main objective of the system of documentation utilized must be to establish, control, monitor and record all activities which directly or indirectly may affect the quality of medicinal products.	The main objective of the system of documentation utilized must be to establish, control, monitor and record all activities which directly or indirectly impact on all aspects of the quality of medicinal products.	The proposed revision is the text from EudraLex Vol 4. It is wider ranging and less ambiguous.
768	Specifications for finished products, in particular	Specifications for finished products which should include or provide reference to	It should be sufficient for specifications to provide reference to some of the expectations rather than have them specified within the document. Revised wording is then consistent with Volume 4.

Line Number	Current Text	Proposed Change	Rationale or Comment
1195, 1197, 1200	Water for injection	Water for injections	Consistency with European pharmacopoeia