European Commission Consultation Paper: GMPs for ATMPs

Comments from:

Name of organisation or individual
PDA (The Parenteral Drug Association)

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
Name	Comment	Decision to Submit/ withdraw comment
	GMPs are a set of processes to regulate manufacturing operations of medicines for patients. PDA believes ATMPs (both investigational and commercial ATMPs) should be manufactured following the same GMP principles as commercial medicinal products, however, because of the complex nature of ATMP products, PDA understands the need to restate some common GMP requirements in a document specific to these products. PDA recommends wherever possible to add reference to existing guidance such as Annexes 1,2, 13 or 15 and that the proposed guidance focus primarily on the unique aspects of ATMPs. The requirements should reflect the nature of the product and risks to patient safety and provide clear standards for both industry and investigators.	
	Although flexibility in GMPs is appreciated for early stage development, the principles and practices should be equally applied to any tissue processing beyond minimal manipulation whether that occurs in a hospital setting or at a manufacturing site. PDA recommends EC establish such consistent GMP standards for use of industry and inspectors to ensure patient safety and product quality.	

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)*
Q2		Yes. Risk- benefit to the patient is a key requirement for ATMP's and PDA finds it useful to have additional level of details regarding the application of the risk-based approach in the guideline. One possible example could be: Meeting GMP requirements may not always be possible, both for clinical research as well as commercial ATMP's. For example, meeting the requirements of sterility as per the EP (sample volumes, number of retains, etc.) is not always possible for gene modified cell therapy product, such as autologous stem cell therapies, due to the number of cells at the end of the manufacturing process and the need to administer as many as possible as in the case of safe engraftment. Therefore the flexibility to allow for a risk assessment on alternative strategies to support the safety of the product is needed. Applying a risk assessment to the strategy to justify the approach to sterility testing is necessary in this case. In addition because of the innovative technologies incorporated in ATMPs and because of the vantage point the reviewers have seeing many technologies applied across disease groups, it would be advantageous to see explicit EC concerns. Risk concerns are especially critical to understand for any of the unique manufacturing and release processes used for ATMP products.	
Q3		This is a complex question that would benefit from direct dialogue between all stakeholders. The question is unclear as to whether the EC is asking whether Directive 2004/23/EC should be used alone, or is the question whether the Directive should be replaced by the JACIE accreditation system or that additional GMPs should be established for the tissue collection practices. In PDA's opinion, Directive 2004/23/EC does not appear appropriate to consider as GMPs. The Directive reads more as good "tissue" handling practices and does not speak to specific requirements that would support or ensure safety and efficacy of the product if the tissues are manipulated in any way. This Directive is not explicit enough as would be expected for GMPs during commercial manufacturing. The legal status of accreditation and the legal ability of third parties to enforce regulations and guidelines would need to be explicitly clarified in order to assess the adequacy of using accreditation as a stand-in for GMPs. Any third party that could be recognized as the quality standard for cell procurement would have to	

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		meet the underlying control principles of GMP. PDA recommends a mechanism must be created for all stakeholders including the EMA Inspectors Working Group, industry, and the CAT to provide input to the third party standards. For commercial products, third party accreditation, in conjunction with sponsor qualification of procurement sites, could provide additional assurance that adequate controls are in place regarding the desired quality of the starting material, the traceability of the cells, training of personnel, adequacy of premises and documentation system, etc. are met and may also serve to meet the principles of GMP. Where possible PDA recommends that the EC take into consideration the guidelines of tissue banks around the world to have consistent global standards for industry.	
104		PDA recommends a change to this section because the risk to quality of the product depends on the sophistication and adequacy of the control strategy. Complexity alone does not always result in a higher risk. **Proposed change**: "…risks to the quality of the product ~~are~~ **may be** greater if there is a complex manufacturing process…"	
110		It would be helpful if some examples could be included in the eventual guidance document relative to the statement "some flexibility in the application of the GMP requirements so that the ATMP manufacturer can implement the measures that are most appropriate having specific characteristic of the manufacturing process and of the product". PDA is willing to help develop some examples if needed.	
115-122		While the point is clear that flexibility is warranted for early phases of clinical studies, it would be helpful to be clearer with respect to what flexibility would be allowed. Even if the ATMP manufacture is performed in an academic or hospital setting, basic controls on the environment and on personnel qualification and performance are expected. PDA also suggests that the flexibility be tied to product knowledge and re-emphasizes that product safety from a microbial content or an adventitious agent standpoint should still be ensured. PDA recommends that facility cleanliness concepts, personnel training, and equipment calibration would still be required and restated.	

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128 Q4		The requirements as laid down in section 3 seem to be standard and probably don't need to be restated. A reference to the existing requirements for GMP can be made here. The main area where section 3 could be further developed is the concept of cross-contamination (lines 147-151).	
144-146		PDA recognizes this language "Where necessary, personnel engaged in production, maintenance, testing and internal controls, and animal care should be vaccinated." Is consistent with Annex 2. However, this guidance does not specify what vaccinations would be appropriate or why. Are there particular risks with ATMP products that justify the call for personnel vaccination here? **Proposed change**: EC should make explicit their rationale for vaccination and provide an explanation or reference to existing standard.	
147-151		This section in the eventual guidance could be further developed with examples focused on the differences in expectation or acceptability (if any) for production of allogeneic cell therapies or autologous with respect to risk of cross-contamination due to personnel. This same comment is valid for lines 162-166 in the following section, but with respect to facility design and facility flows. PDA is willing to help develop examples if needed.	
157 Q5		The requirements as laid down in section 4 seem to be akin to the manufacture of other biological products (Annex 2) and probably don't need to be restated unless there are unique concerns for ATMPs above and beyond those found in Annex 2. A reference to the existing requirements for GMP can be made here. The main area where section 4 could be further developed is by providing guidance on expectations for control levels when manufacturing different cell products (allogeneic vs. autologous) and including some examples or points for the manufacturer to consider as they design and control their facility.	
157 Q6		Below are some additional flexibilities related to ATMPs manufactured for commercial purposes that PDA recommends could be applied: • Small-scale manufacture: since ATMP products could be manufactured on a very small scale (e.g. for a single, small-volume manufacturing procedure for a single patient), the extent of GMPs should be relatively flexible to assure control and safety while not discouraging innovation. • Closed manufacture/isolators: The extent of prescriptive GMP guidance needs to be balanced with the	

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		risk to patient safety. Closed manufacturing or the use of isolators can capably mitigate much of the contamination risk associated with aseptic manufacturing thus the GMPs should be flexible to allow these innovations. • Automation: GMPs for automated processes used in manufacturing or testing ATMPs should weigh the risks to patient safety against any benefits gained. GMPs should be flexible to allow for these innovations. • Manufacture in hospital/clinical or pharmacy setting: Due to the nature of ATMP treatments, it is easy to imagine ATMP production and testing could be conducted in a hospital or clinical setting. The GMP requirements should be sufficient to assure patient safety and product efficacy yet flexible enough to allow for these innovations.	
157 Q7		PDA has the following recommendation related to investigational ATMPs: The level of GMP control should reflect the level of risk to patient safety and product efficacy. Early clinical studies (e.g. first-in-man) should reflect appropriate caution balanced with not discouraging innovation. A later pivotal clinical trial should use a stable production process intended for subsequent production runs, as is the case for traditional drugs and biologicals. Another factor to consider is the nature of the product; autologous ATMPs will likely have a more favorable risk profile than an allogeneic or xenogeneic product.	
214-215		*PDA requests attention be paid to the use of terms "qualification" and "validation" to be consistent with international norms.* Premises are qualified, not validated. Processes are validated.	
240		Not only "large scale" production, but small-scale too should have adequate drains. PDA recommends deleting the phrase "large scale". PDA suggests: Drains should be of adequate size, and have trapped gullies.	
231-233		PDA recommends the following text be added for clarification: "In general, an A grade with a background of B grade is required for pivotal clinical trials and commercial production **for areas where sterile product or sterile product contact surfaces are exposed**."	

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233 Q8		It is not clear why gene therapy investigational medicinal products would have an exception. A procedure that takes place entirely in an isolator (Grade A) or in an entirely closed manufacturing system can be located in an area with a C or D grade because the aseptic conditions are maintained by the equipment itself and not by the room where it is located. This should be true whether it is in an early phase of clinical trials or in commercial production. All incoming and exiting air would need to be filtered. Filters and ports that are used to add materials (including solvents, excipients, and rinses) need to incorporate a process (such as steaming the port or valve) in the procedure to assure the product does not get contaminated. Personnel changing the filters need to wear appropriate protective gear to protect themselves and the product.	
Q9 & Q10		The requirements as laid down in section 5 seem to be akin to the manufacture of other biological products (Annex 2) and probably don't need to be restated unless there are unique concerns for ATMPs above and beyond those found in Annex 2. A reference to the existing requirements for GMP can be made here. PDA did not identify equipment or documentation guidance for ATMPs above and beyond what is already found in Annex 2.	
Q11		ATMP's manufactured for commercial use would follow the same principles regarding quality systems as more traditional pharmaceuticals. For example, a Quality Management system, which includes CAPA, Change Control, Documentation Control, Batch Records, Excursion and Investigation Records etc., would still apply to ATMP's. There may be some difference in application, but the principles would be the same. Per line 440, the expectation that records be kept for a minimum of 30 years after product expiry, is very lengthy, thus there should perhaps be some flexibility in the amount of documentation kept per batch. For example, retaining only final product records (as long as all materials can be traced back to their source) rather than retaining all incoming and processing records for the entire retention period. Traceability will remain an important concern for ATMP products thus documentation should underscore this.	
Q12		Regardless of where the Investigational ATMP's is formulated, traceability will remain an important concern and thus the documentation should underscore this. The principles and practices of a Quality System for investigational ATMPs should be commensurate with the level of risk.	
330-333		It is clear that changes which have an impact to the process or the product need thorough evaluation and may require competent authority agreement, but if the document could provide more substantive description or some examples of what would be considered "substantial modifications" for investigational	

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		ATMPs, it would be helpful to include them in this document.	
336-344		If the raw materials used (such as cytokines, or other biological materials) are covered by an approved Market Authorization, it should be acceptable to rely on C of A and not need to repeat testing.	
382-386		Requirements of Annex 13 should be referenced. While it may be acceptable for records limited to information of relevance to activities in respective locations to be under the oversight of "local" QPs, the suggested language does not address if there should be a comprehensive review of the manufacturing steps in their entirety against the product specification. This should be ensured.	
423		PDA recommends clarification with the use of terms "qualification" and "validation" and recommends the following revisions to the text. **(i) Validation of processes and analytical methods or Qualification of equipment and premises.**	
427-431		Clarity with the requirements from Annex 2 should be assured. It is not clear what "Batch documentation" is referred to on Line 427 as related to ATMP products (which by definition are gene therapies, somatic cell therapies (consists of cells or tissues that have been subject to substantial manipulation), tissue engineered products, or combined ATMPs). Annex 2 indicates that "where human cell or tissue donors are used, full traceability is required from starting and raw materials, including all substances coming into contact with the cells or tissues through to confirmation of he receipt of the products at the point of use" are required to be maintained for 30 years.	
Q's 13, 14, 15, 16, 18, 19, 20, 21		The requirements as laid down in these sections seem to be akin to the manufacture of other biological products (Annex 2) and in PDA's opinion don't need to be restated. A reference to the existing requirements for GMP can be made here. The eventual guidance should focus on unique concerns for ATMPs above and beyond those found in Annex 2.	
Q13		In addition to the above recommendation to focus on unique requirements for ATMPs, section 7 could be further developed by providing guidance on requirements with regards to retain samples, particularly for autologous product with limitations on the amount of available material.	
485		Prior to stating that where possible, sterilization of starting materials and raw materials should be performed by heat, it is important to stress that the sterilization process should be shown to be effective	

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		both in removing or reducing the contaminants and preserving the activity of the material (particularly for raw materials and excipients). As in other parts of the document, the guidance should be based on applying knowledge of the material and appropriate evaluation for risk. All of the techniques can be considered as effective when appropriately applied and verified, and therefore, one should not be emphasized over another.	
Line 677 - 689 Section 9.5 and 9.6		Further guidance on final product label requirements, particularly for autologous products, would be helpful	
Q17		The principles of process validation could be applied using a risk-based approach. Validating the process includes validation throughout the supply chain (starting materials through drug product itself, including methodologies). ATMP's pose several challenges, which will require control strategies based on a risk assessment approach. Identifying analytical markers (or surrogate markers) reflecting critical quality attributes and testing for them either in situ or as part of the release for the ATMP product (even if part of an abbreviated release process) could serve as an alternative to process validations. Aspects of the process that can impact the safety profile (e.g. preventing or eliminating impurities) may need extensive process development studies and perhaps validation for those critical steps.	
Q22		It behooves the manufacturer to design a robust "reconstitution" process where the product is buffered from poor handling or technique by the healthcare provider(s) at the patient site. Human factors testing can contribute valuable inputs into the design process.	
Q23		Yes. It is analogous to the reconstitution of a freeze-dried product by a healthcare provider at the bedside of the patient.	
Q24		If the term "reconstitution" is used, it should require a clear definition. PDA recommends the term be limited to those steps where a product is transformed from one physical state (e.g. a solid) to another physical state (e.g. a liquid). According to this definition of the term, diluting or mixing the ATMP with the patient's own cells and/or other substances added for the purposes of administration (including matrixes) would not be considered "reconstitution". PDA recommends instead, "diluting" or "mixing" or "seeding a matrix" should be defined specifically for the act that is performed.	
Q25		The primary concern for identifying the applicability of specific GMP guidance should be the potential risk	

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		to patient safety and product efficacy. It behooves the manufacturer to design a robust automated device or system where the product and the processes conducted are protected from poor handling or technique by the healthcare provider(s) at the hospital or patient site. Human factors testing can contribute valuable inputs into the design process.	