Lonza

Response to Targeted Stakeholder Consultation on the development of Good Manufacturing Practice for Advanced Therapy Medicinal Products pursuant to Article 5 of Regulation 1394/2007

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1. Introduction

Lonza welcomes the opportunity to review and provide feedback on the European Commission draft proposals on the development of Good Manufacturing Practice for Advanced Therapy Medicinal Products ("ATMPs") pursuant to Article 5 of Regulation 1394/2007.

Lonza is one of the world's leading suppliers of active pharmaceutical ingredients (APIs) and biopharmaceuticals, as well as research and testing products and services. Lonza customers cover a wide spectrum of clients, from the world's largest pharmaceutical and biotechnology companies to medical research and testing organizations to small start-ups pioneering breakthrough medical treatments.

Lonza is also a leading contract manufacturer of cell and gene therapy products, with facilities in Singapore, and Houston and Walkersville in the US, supplying a broad range of customers with investigational ATMPs for use in clinical studies which are run by our customers in the EU and globally. Lonza is therefore engaged in both the development and manufacture of ATMPs.

Lonza is committed to supporting customers in the development through to commercial supply in a rapidly developing field and recognises the need to ensure that adequate GMP requirements are in place to ensure patient safety and product consistency with regard to all ATMPs.

2. Overview

Lonza's comments concern the following areas.

The existing GMP requirements set out in Eudralex Vol 4 and in the ICH guidances are generally applicable to the development, manufacture and control of ATMPs, notwithstanding the unique nature of these products. In view of this Lonza considers that the level of detail provided in the draft guidance is not sufficient, and that there should be greater use of existing and well established guidances to ensure patient safety and product consistency and quality.

In the process of developing guidance that may be specifically applicable to ATMPs, in view of the international approach to product development, due consideration should be given to discussion with other organisations and agencies such as FDA, PMDA and ICH.

3. Response to questions

3.1. Introduction

Lonza agrees that compliance with Good Manufacturing Practice is essential to ensure the quality and safety of medicinal products at all stages of the product lifecycle. Lonza considers that the GMP requirements in Eudralex Vol 4 are appropriate for ATMPs.

3.2. GMPs for ATMPs: general principles

Q1: Are the principles laid down in Section 2 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e.first-in-man clinical trials?). Please provide comments on the text below as appropriate.

Lonza Response

The principles of GMP should be the same for investigational ATMPs as they are for conventional medicinal products. The IMPD defines the process and must be adhered to so as to ensure product safety and consistency with regard to quality. Reference should be made to the Eudralex Vol 4 and relevant annexes.

For Commercial products, the same GMP principles should apply as are applied to conventional medicinal products. Requirements of the Marketing Authorisation to be followed, and Eudralex Vol 4 Annexes applies.

Q2: Do you consider it useful that additional level of detail regarding the application of the risk-based approach is provided in the Guideline? In the affirmative, please provide examples.

Lonza Response

For investigational material: A risk-based evaluation of processes is a key part of GMP and is therefore appropriate. However, this should not replace the need for the application of the principles of GMP to apply to ATMPs used in clinical studies. Rather, more a risk-based approach should be supported. There should not be a difference in quality systems used by commercial manufacturers vs. those used in hospitals or academia (i.e., no two tier system). It is important that for early stage clinical trials, sufficient control of the product is established for all patients in the study to receive a safe and consistent product, again this follows the same principle as is applied to conventional medicinal products.

For Commercial products where a process is fixed and the product is well defined, a risk based approach may assist in evaluation of deviations to that process.

Q3: How should the quality systems established in accordance with Directive 2004/232 be recognised in terms of GMP compliance for products that are ATMPs solely because the use of the relevant cells/tissues is for a different essential function in the recipient as in the donor (i.e. the manufacturing process

does not involve any substantial manipulation)? What about the JACIE accreditation system?

Lonza response

No comment.

3.3. . Personnel

Q4: Are the requirements laid down in Section 3 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?). Please provide comments on the text below as appropriate

Lonza Response

For the manufacture, testing and release of Ph. I/II clinical material more details should be added and these details should be consistent with and inclusive of the requirements for Personnel as stated in Eudralex Volume 4, Annex 1 as ATMPS are generally manufactured using aseptic processes and the sterility of the final product is most important for clinical subject safety. Some elements of Eudralex Volume 4, Chapter 2 should also be included, examples are the following. Line 131 and Line 152-156: add a requirement that the responsibilities should be documented. Line 133: add a requirement that training should include the principles of microbiology and aseptic processing. Line 138: Add a requirement that only the minimum number of personnel required should be present in a clean manufacturing area and that personnel shall not wear wristwatches, jewellery, make-up, nail polish. A description of hygiene and washing and the clothing required in each clean area and rooms leading to them should be described per Annex 1.

For Phase III /commercial manufacturing: The requirements as described in Section 3 are too general and do not provide sufficient detail for the GMPs necessary for the manufacture of Phase III clinical and commercial products. The current Eudralex Volume 4 Chapter 2 and Annex 2 pertaining to biological products and Annex 1 pertaining to Sterile and Aseptic products are applicable to ATMPs and appropriate and detailed requirements are given in those documents. Therefore, current EU cGMPs should be used for the Personnel requirements.

3.4. Premises

Q5: Are the requirements laid down in Section 4 sufficiently well-adapted to the specific characteristics of ATMPs? Please provide comments on the text below as appropriate.

Lonza Response

Yes, although more detail regarding the required air classifications would be appreciated. Current Eudralex GMPs will apply.

Q6: Do you consider that there are additional flexibilities that could be applied in connection with the requirements related to premises without compromising the quality of the ATMPs manufactured for commercial purposes?

Q7: Do you consider that there are additional flexibilities that could be applied in connection with the requirements related to premises without compromising the quality of investigational ATMPs? If appropriate, please consider possible differences

Lonza Response to Q6 and 7

For investigational ATMP material there could be flexibilities, but this document does not include sufficient guidance for manufacturers or Qualified Persons to consistently apply the expectations which could lead to inconsistent application and interpretation of the guidance. Any sterile product to be injected should be handled by technically qualified personnel in well-controlled and monitored facilities of the appropriate cleanliness level. For commercial production there should not be flexibility from current regulatory requirements.

Q8: Should the use of a clean room with an A grade with a background of C or D grade be allowed for early phases of clinical trials (with the exception of gene therapy investigational medicinal products), provided that the specific risks are adequately controlled through the implementation of appropriate measures? Please substantiate your response. In particular, if you consider this option should be introduced, please address the benefits of introducing such flexibility and explain what measures could, in your view, be applied to avoid cross-contamination having regard to the potential risks (e.g. the level of cell manipulation, the use of processes that provide extraneous microbial contaminants the opportunity to grow, the ability of the product to withstand purification techniques designed to inactivate or remove adventitious viral contaminants, etc.)

Lonza Response

For both clinical and commercial production: Open manipulations during the manufacturing process should always be carried out in a Grade A environment with a Grade B background. Regarding manufacturing in a Grade C or D environment: this should be reserved for processes using completely closed systems where there are no open manipulations. Examples of closed systems would be clean weld connections or use of certain designs of sterile connectors.

3.5. . Equipment

Q9: Are the requirements laid down in Section 5 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trial)? Please provide comments on the text below as appropriate.

Lonza Response

It is expected that all equipment used for ATMPs in commercial manufacture will be validated and suitable for its intended use. Current EU GMPs should apply.

3.6. Documentation

Q10: Are the requirements laid down in Section 6 sufficiently well-adapted to the specific characteristics of ATMPs? Please provide comments on the text below as appropriate.

Lonza Response

Current Eudralex requirements for documentation should apply

Line 420 - should consider the stage of manufacture; principles are well defined in Annex 15; more detail for cell therapy/autologous type products in Annex 15 could be added

Q11: Do you consider that there are additional flexibilities that could be applied – without compromising the robustness of the quality system- in connection with the documentation obligations for ATMPs manufactured for commercial purposes?

Lonza Response

No flexibilities should apply. Established Guidance, for example ICH Q10 should be used in the development and management of Quality Systems, including documentation requirements**.**

Q12: Do you consider that there are additional flexibilities that could be applied – without compromising the robustness of the quality system- in connection with the documentation obligations for investigational ATMPs? If appropriate, please consider possible differences between first-in-man clinical trials and pivotal clinical trials

Lonza Response

See response to Q 11**.**

3.7. .Starting and raw materials

*Q13: Are the requirements laid down in Section 7 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trial)? Please provide comments on the text below as appropriate***.**

Lonza Response

This section discusses in detail requirements for starting materials but more information is needed for raw materials. Existing regulations and standards outlined in USP and EP are well suited for ATMPs.

Line 459 - more information required on establishing quality requirements for starting materials; Tissue acquisition regulations are already in place. However, more guidance may be needed for autologous sources of starting material.

3.8. .Seed lot and cell bank system

Q14: Are the requirements laid down in Section 8 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trial)? Please provide comments on the text below as appropriate.

Lonza Response

Yes. As written these are straightforward requirements and are consistent with current practice in the manufacture of other types of biologics.

For clinical material manufacture it may be acceptable to store different seeds and/or cells in the same area or in the same equipment if sufficient controls are in place to prevent mix-up and takes into account the risks inherent with the infectious nature of some materials to prevent cross-contamination.

3.9. Production

Q15: Are the requirements laid down in Section 9 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?)? Please provide comments on the text below as appropriate.

Lonza Response

Section 9.1, General Principles, line 580 mentions that necessary in-process and environmental controls should be carried out and recorded. This section should include examples of such controls. In addition, details surrounding Environmental Monitoring/Particle Monitoring requirements are insufficient and compliance with Volume 4, Annex 1 should be a clear requirement, for both clinical and commercial operations. Line 565 should be clarified to require deviations to be raised if unexpected observations, non-routine interventions, or accidental spills occur during production.

Section 9.2, Handling of incoming materials and products, should specify that containers and materials likely to generate fibres should be minimized in clean areas. Recommendation for use of paper records in production areas should also be included – require paper records and other items to be autoclaved. Line 599-601 mentions sterilization of materials prior to use in manufacturing; this section should include validation requirements for the treatment of materials in this manner. It would be helpful if this section included an evaluation of which items must be sterilized prior to entry in the Grade B area.

Section 9.3, Prevention of cross-contamination in production should include requirement for handling of waste in a unidirectional manner.

Section 9.4, Other Operating Principles: cell culture vessels (flasks, cell factories, bioreactors) typically contain sterile filters to permit gas exchange. It is recommended that appropriate and risk-based filter integrity testing requirements be included.

Section 9.5, Packaging materials, should include requirements surrounding final product label use and reconciliation, similar to 5.55 , 5.56, 5.58, 5.61 and 5.62 of Eudralex Vol. 4, Chapter 5: Production.

General comment: Eudralex Vol. 4 Annex 1 provides sufficient guidance for aseptic operations. However for ATMPS there are some materials that would enter the Grade B space that cannot be sterilized and rely on surface decontamination.

3.10. Qualification and validation

Q16: Are the general principles laid down in Section 10 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?)? Please provide comments on the text below as appropriate.

Lonza Response

This section should include additional details on validation of aseptic processing, including design of validation studies, frequency of requalification, etc. This applies to both commercial and clinical manufacturing. Eudralex Vol. 4 Annex 1 applies in this case to ensure sterility of the product. More detail could be included in Annex 1 for ATMPs.

Q17: Due to the biological variability inherent in ATMPs and limited batch sizes, process validation is particularly challenging for ATMPs. A pragmatic approach as to the specific requirements on validation should be developed. Please provide suggestions.

Lonza Response

For clinical trial material there should be a clear requirement that for sterile products, validation of sterilising or aseptic process should be of the same standard as for commercial products, as required by Eudralex Volume 4, Annex 13. Any processing steps or test methods to assure the safety of the ATMP should be validated. Critical process parameters along with in-process controls should be identified during development to provide adequate assurance of lot to lot consistency.

3.11. Qualified person and batch release

Q18: Are the requirements laid down in Section 11 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of

development, i.e. first-in-man clinical trials)? Please provide comments on the text below as appropriate.

Lonza Response

There should be a clear delineation of what is expected for release of clinical trial material. Eudralex Volume 4, Annex 13 provides good detail on what is required and should be considered for release of clinical material. Those elements should be included here or referenced.

There should be clear delineation of what is required for commercial product release. This section is in substantial agreement with the current requirements defined in Eudralex Volume 4, Annex 16 and the new version of that document. There should be no difference in how ATMPs and other medicinal products are handled and released by QPs, the same requirements apply.

Line 756-757 for testing of autologous or short expiry products: the MA should specify if third country testing is authorized and the laboratories should be specified. Use of laboratories in other regions will need to be considered for these types of products**.**

3.12. Quality control

Q19: Are the requirements laid down in Section 12 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e.first-in-man clinical trials?)? Please provide comments on the text below as appropriate.

Lonza Response

These subjects are covered sufficiently in current Eudralex Part 1 which should apply.

Line 928: Primary packaging; samples should be retained.

Line 985: For clinical/ development material it is essential to trend quality attributes to ensure the process is understood and improved throughout the development of the product/

Line 1002 Stability data should be required for MAA

3.13. Outsourced activities

Q20: Are the requirements laid down in Section 13 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?)? Please provide comments on the text below as appropriate.

Lonza Response

This subject is sufficiently covered already in Eudralex Part 1 and there should be no special requirements for ATMPS.

3.14. Quality defects and product recalls

Q21: Are the requirements laid down in Section 14 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?)? Please provide comments on the text below as appropriate.

Lonza Response
These topics are already covered sufficiently in Eudralex Vol. 4 and there should be no special or separate requirements for ATMPs.

3.15. Environmental control measures for gene therapy products

Lonza Response
No additional comments

3.16. Reconstitution of product after batch release

Q22: Do you agree with the principle that, where reconstitution of the finished ATMP is required, the manufacturer's responsibility is limited to the validation of the process of reconstitution and the transmission of detailed information about the process of reconstitution to the users?

Lonza Response
Yes

Q23: Do you agree with the principle that reconstitution is not manufacturing and therefore is outside GMP?

Lonza Response

Yes

Q24: What activities should, in your view, be considered as reconstitution?

Lonza Response
Reconstitution should be defined as activities which are specific to prepare the product for administration to the patient after the final product has been released by the ATMP manufacturer.

17. Automated production of ATMPs

Q25: How do you think that the GMP obligations should be adapted to the manufacture of ATMPs through the use of automated devices/systems? Who should be responsible for the quality thereof?

Lonza Response

Automated systems for processes leading to, or contributing to the production of an ATMP should be considered manufacturing equipment, and not medical devices. Manufacturing equipment should be selected, installed, qualified and

maintained under the necessary GMP requirements by the ATMP manufacturer. Suppliers should be selected who maintain a Quality system sufficient to document and maintain equipment design history, control of changes to the equipment, appropriate qualification and control of suppliers of equipment parts and disposables, complaint handling, and demonstrated manufacturing process control. The level and details of the quality system are defined under the relevant ISO standards.

In addition to properly selecting equipment, the ATMP manufacturer has responsibility for the GMPs in the use of automated equipment, and therefore should apply relevant sections of Eudralex Volume 4 for manufacturing. The ATMP manufacturer should qualify the equipment supplier and then continue to monitor through periodic audits and routine monitoring of equipment and process performance. The ATMP manufacturer should be responsible for validating the process for which the automated equipment is used and then continually monitoring the process.