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GMP/GDP Inspectors Working Group (GMP/GDP IWG) Concept paper on the revision of Part IV Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products

Agreed by GMP/GDP IWG	15th April 2025
Start of public consultation (if applicable)	8th May 2025
End of consultation (deadline for comments)	8th July 2025

The proposed guideline will replace:

- 'Eudralex Volume 4: Part IV GMP specific to ATMP'

Those participating in the public consultation are asked to please submit comments via the EU Survey tool at the following **link**

Keywords	GMP, sterile, annex 1, ATMP,

1. Introduction

This concept paper aims to outline the rationale, objectives, and proposed changes for updating Part IV – GMP specific to ATMP of the good manufacturing practice (GMP) guide Eudralex Volume 4 following the revision of Annex 1 which came into operation in August 2023. As the Part IV is an EU standalone guideline and that the sector is to abide solely for reference, it should be revised independently to address recent developments in the manufacture of sterile medicinal products.

Since the introduction of the revised GMP Annex I for the manufacture of sterile products has modified and clarified some requirements compared to the current ATMP guideline, the proposed revision of the ATMP guideline is to align with the current Annex 1 while maintaining a flexible approach for the production of ATMPs.

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2. Discussion

Part IV was developed under the initiative of the European Commission according to Art 5 of the Regulation (EC) No 1394/2007 and was adopted on November 22, 2017. After extensive consultations with the stakeholders, the European Commission had deemed it necessary to reflect the entire requirements for the manufacture of ATMPs in one single guideline, moving away from the former Annex 2 Manufacture of Biological active substances and Medicinal Products for Human Use, and all pertinent chapters of the Eudralex Volume 4 guideline. The rationale was to allow academia, developers and manufacturers to achieve the consistent production of high-quality ATMPs across the European Union.
Since the release of the revised Annex 1, the incorporation of relevant ICH concepts (such as Quality Risk Management (QRM) and Pharmaceutical Quality System (PQS)), the introduction of Contamination Control Strategy (CCS), and recent technological advancements are not yet reflected in the current ATMP GMP guideline.
EudraLex Part IV contains only requirements for applying a risk-based approach in all the sections of the guidance, however the revised Annex 1 is referring to Quality Risk Management (QRM) principles with reference to ICH Q9 concepts that offer a more systematic approach to quality risk management, and to ICH Q10 which describes a modern pharmaceutical quality system (PQS) which allows to establish and maintain a state of control of product quality and to facilitate continual improvement over the entire life cycle, which is also the basis for the Contamination Control Strategy (CCS).
In addition, the current ATMP guideline does not reflect the advances of new technologies in the manufacture of advanced medicinal products; the proposed revision will give further clarifications on the expectations how to qualify, control and manage clean rooms and closed systems (isolators and Restricted Access Barriers Systems (RABS) in order to prevent detrimental impact on product but it will maintain open to the use of biosafety cabinets due to of the numerous manual manipulations associated with the individualized batches .
The proposed revision will embrace the use of new technologies that are not currently covered in the current version (e.g. automated advanced technology, (closed) single use systems, fast rapid microbiological testing methods).

Following the publication of a new regulation on standards of quality and safety for substances of human origin intended for human application there is also a need to update legal references and definitions for the starting material of human origin.

It is noted that the current revision will only focus on the sterile manufacture sections related to the updated version of the Annex 1 and not to update any other topics/sections outside of that scope.

3. Recommendation

The working group action plan was presented to the GMP/GDP Inspector's working group on the 26th of November 2024. The GMP/GDP Inspectors Working Group recommends that the current version of ATMP guideline is revised to align with the recent revised Annex 1.
The new guideline should clarify how manufacturers can take advantage of new possibilities deriving from the application of an enhanced process understanding by using innovative tools as described in the ICH Q9 and Q10 guidelines.
The revised guideline will seek to remove ambiguity and inconsistencies and will take account of advances in technologies.
The working group action plan was also presented to the BWP and the CAT on the 22nd of January 2025.

4. Proposed timetable

Preparation of draft concept paper - January 2025
Approval of draft concept paper – 15th April 2025
Released for consultation – 8th May 2025
Deadline for stakeholders' comments – 8th July 2025
Proposed date for release of draft guideline – September 2026
Deadline for stakeholders comments - December 2026
Adoption in GMDP IWG - March 2027

5. Resource requirements for preparation

A drafting group has been established, with a kick-off meeting held on the 30th of November 2024. Meetings are schedule every 2 weeks in order to closely monitor the progress on work. Regular feedback will be provided to the GMP/GDP IWG. Feedback from CAT will be requested once the first draft is available.

6. Impact assessment (anticipated)

There is no anticipated adverse impact on the industry in terms of resources or costs. However, clarifying the use of new systems may necessitate gradual modifications to certain facilities, equipment, and processes over time.

Revision of the guideline will facilitate a better understanding of expectations which will lead to more consistent and improved manufacture of ATMPs.

7. Interested parties

EMA (GMP/GDP Inspectors Working Group, Committee for Advanced Therapy, Biologics Working party), national competent authorities of EU/EEA member states, stakeholders.

References to literature, guidelines, etc.

ICH Q9 Quality Risk Management
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002873.pdf
ICH Q10 Pharmaceutical Quality System
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002871.pdf
GMP guide to good manufacturing practice for medicinal products annex 1
http://ec.europa.eu/health/files/eudralex/vol-4/2008_11_25_gmp-an1_en.pdf

Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal products
https://health.ec.europa.eu/system/files/2019-10/atmp_guidelines_en_0.pdf