

Final Concept Paper

Q5E Annex EWG: Comparability of Advanced Therapy Medicinal Products (ATMPs) Subject to Changes in Their Manufacturing Process

[Annex to ICH Q5E]

Endorsed by the Management Committee on [02/June/2026]

1. Background to the proposal and statement of the perceived problem

- ICH Q5E provides a science- and risk-based framework for demonstrating comparability of biotechnological/biological products following manufacturing process changes. ICH Q5E was adopted in 2004, and its fundamental principles remain applicable. However, the emergence of advanced therapy medicinal products (ATMP) has highlighted the need for additional guidance. Following comprehensive discussion within the ICH Cell and Gene Therapy Discussion Group (CGTDG), development of an Annex to ICH Q5E was recommended to address ATMP-specific considerations.
- Evaluating the comparability of ATMPs after a manufacturing change is essential to ensure that the change does not adversely impact product quality, safety, or effectiveness. However, the unique complexity of many ATMPs represents significant scientific challenges in achieving this goal. Specifically, comparability assessments may be constrained by several factors (e.g., inherent variability of starting materials, limited product availability, patient-specific aspects). These factors complicate developers' and regulatory authorities' efforts to assess comparability across regions, and this can result in extended development timelines and/or increase costs for resource-intensive programs. Regulators may encounter review burden when applying comparability principles to highly complex ATMPs, where scientific uncertainty and limited characterisation can lead to variability in interpretation across regions. Patients may experience delayed availability of these therapeutics, or potential safety impacts if beneficial manufacturing or product quality improvements are not implemented. Conversely, patients may face significant risks if a post-change product is administered and has undetected adverse impacts on safety or efficacy due to an inadequately designed or inconclusive comparability study.
- The fundamental objective of this Annex is to facilitate the consistent maintenance of product quality, safety, and efficacy through science-based comparability assessments, adapted for the unique aspects of ATMPs. The Annex should establish globally harmonised science- and risk-based approaches for assessing comparability across a broad range of ATMP complexities following manufacturing changes. Comparability exercises are essential throughout the product lifecycle, including during development and post-approval. In cases where an ATMP incorporates or is specifically combined with a medical device or delivery system, or there is a matrix for cell- or tissue-based products, additional testing may be necessary for the combined product during the comparability exercise.
- Refer to the following publications:
 - *Recommendations with regard to future ATMP related Guidelines: Output from cell & gene therapy discussion group (CGTDG) (2023-2025), ICH*
 - *Questions and answers on comparability considerations for advanced therapy medicinal products (ATMP), EC, Europe 2019*

- *Manufacturing changes and comparability for human cellular and gene therapy products, FDA, United States 2023*
- *Guideline for comparability of human cell-processed products subject to changes in their manufacturing process, MHLW/PMDA, Japan 2024*
- *Technical Guidelines for the study and evaluation of CMC changes in cell therapy medicinal products, CDE/NMPA, China 2026*
- *Guideline on comparability assessment of investigational cell and gene therapy products, MFDS, Republic of Korea 2026*

2. Type of harmonisation action proposed

The proposed ICH procedure is considered a revision of ICH Q5E: Comparability of biotechnological/biological products subject to changes in their manufacturing process. The concept paper outline was endorsed by the ICH Assembly on 13 May 2025. The proposed Annex will complement the content of ICH Q5E and address considerations for a wide range of ATMP complexities without modifying the core guidance document.

3. Issues to be resolved and expected deliverable(s)

The Expert Working Group will aim to address the following issues:

- The Annex will complement the ICH Q5E Guideline and address key challenges faced when assessing comparability of ATMPs following manufacturing changes (high-level principles and detailed technical guidance).
- A strict application of conventional comparability approaches may not be suitable for all ATMPs. The Q5E Annex aims to enable fit-for-purpose (scientifically justified and risk-informed) comparability approaches to address ATMP-specific challenges such as limited product availability, product complexity, inherent variability of starting materials (e.g., patient-specific aspects), and methodological limitations. Holistic science- and risk-based approaches can be appropriate due to the nature of ATMPs. In situations where traditional analytical methods are not feasible due to inherent ATMP characteristics, scientifically justified fit-for-purpose approaches may be necessary. These approaches should leverage the totality of available evidence, including innovative analytical technologies, to provide a high degree of confidence in post-change product quality.
- Fit-for-purpose approaches which can be justified using science- and risk-based approaches might need to be considered in cases including but not limited to:
 - Novel and/or innovative manufacturing approaches that require tailored strategies for assessing comparability (detailed technical guidance).
 - Highly complex ATMPs with limited ability to characterise the product (e.g., cell-based and tissue-based products) (high-level principles and detailed technical guidance).
 - Individualised ATMPs manufactured for a specific patient with corresponding batch-to-batch variation; potential need to leverage surrogate materials.
 - Few product batches available, limited manufacturing experience, and limited patient exposure that may be encountered with ATMPs for treatment of rare diseases.
- The relevant information will fit into CTD and M4Q formats.

Scope of the issues to be resolved:

- The scope of the Q5E Annex will include a wide range of ATMP considerations and product modalities (as defined in WHO TRS1048 Annex 3 issued in 2023). ATMPs include cell and gene therapy products and tissue-based products, such as nucleic acid-based gene therapy products, viral vector-based gene therapy products, genetically modified somatic cells, stem cell-derived products (e.g., induced pluripotent stem cell-derived), and gene editing products. The considerations outlined in the annex might also apply to other product types.

Deliverables:

- The main deliverable is an Annex that complements the parent ICH Q5E Guideline and addresses special considerations and fit-for-purpose approaches when assessing ATMP comparability.
- There will also be supportive training material to illustrate the application of fit-for-purpose approaches to various subclasses of ATMPs because applying the comparability principles across widely diverse ATMP modalities can be challenging.

4. Planning

4.1. Resources and Expertise

- Expert knowledge is required in the quality of biological products and advanced therapy medicinal products, including manufacturing processes and controls, raw materials, impurities, specifications, potency, analytical methods, and stability. The focus of the Annex will be on quality aspects. Non-clinical and clinical expertise will be relevant for high level principles only. Expertise in non-clinical aspects includes pharmacokinetics, immunotoxicity, and novel *in vitro* methods. Expertise in clinical aspects includes clinical trial design, post-approval evidence generation, and long-term follow up.

4.2. Planned Interactions/Data Generation

- Feedback from the ICH Q1 EWG and the ICH Q6(R1) EWG is anticipated to ensure alignment with updated expectations for ATMP stability and specifications, respectively.

4.3. Timeframe and Key Milestones

Key Milestone	Estimated Timeframe
Finalise Concept Paper, Work Plan	June 2026
Step 1 sign-off of ICH Q5E Annex Technical Document by EWG Topic Leaders/ Step 2 a/b Assembly endorsement of draft ICH Q5E Annex Guideline and release for public consultation (6 months, including 120 day comment period)	August 2027
Begin development of Q5E Annex EWG Training Materials/Stakeholder Engagement etc.	June 2027

<i>Step 3 documents and sign off draft Q5E Annex / Step 4 adoption of Final Q5E Annex</i>	January 2028
<i>Step 4 ICH Assembly Regulatory Members adopt Final Q5E Annex</i>	February 2028

5. Impacts of the project and post-hoc evaluation

The objective of the proposal is to establish a globally harmonised science- and risk-based approach for assessing comparability across a wide range of ATMP complexities following manufacturing changes. Developers are expected to benefit from better aligned expectations for comparability studies across regions, clearer requirements for planning and implementing manufacturing changes throughout the product lifecycle and streamlined global development programs. Regulators are expected to benefit from a scientifically consistent evaluation framework that may, where appropriate, facilitate reliance and work-sharing within existing regulatory frameworks, as well as reduced review burden via harmonised expectations, and the ability to provide consistent recommendations across regions. Patients are expected to benefit from more rapid availability of innovative therapeutic products through improved development and manufacturing efficiency, improved product supply through manufacturing optimisation and capacity expansion, and consistent maintenance of safety and quality through science-based comparability assessments.

The challenges of evaluating comparability of pre- and post-change ATMPs are currently recognised in national/regional guidelines. Effective assessment of comparability is essential to maintaining continuity throughout the lifecycle of a biological product. Alignment of scientifically justified fit-for-purpose approaches is needed, including holistic approaches that rely on the totality of evidence and the appropriate use of statistical analyses. The Annex is expected to harmonise principles and expectations for comparability assessments while providing flexibility for science- and risk-based approaches that can be implemented within existing legal and regulatory structures.