**RECOMMENDATIONS WITH REGARD TO FUTURE ATMP RELATED GUIDELINES**

**OUTPUT FROM CELL & GENE THERAPY DISCUSSION GROUP (CGTDG) (2023-2025)**

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## INTRODUCTION

The development of advanced therapy medicinal products (ATMPs) has progressed over the past several years, and the field continues to see the emergence of many new therapeutic modalities. ATMPs, which encompass cell and gene therapy (CGT) products, are often transformative medicinal products to treat conditions for which there are limited or no other treatment options or to treat the underlying cause of disease.

The growing global development of ATMPs is reflected in the large number of regional guidelines specific to these products. An analysis conducted by the ICH Cell and Gene Therapy Discussion Group (CGTDG) in December 2024 indicated that more than 300 ATMP-specific guidelines had been issued in draft or final form by ICH members and observers represented in the CGTDG (see Annex II below). This growing number of region-specific guidelines underscores the need for harmonised global regulatory and development approaches.

At this time, there is one finalized ICH guideline dedicated to ATMPs, namely, ICH S12 Nonclinical Biodistribution Considerations for Gene Therapy Products [1] though this does not recommend approaches to testing for genomic integration or off-target editing, which are important for many ATMP products. ATMPs are mentioned in several ICH guidelines (e.g., ICH E2F[2]; ICH Q5A(R2) (Annex 6)) [3] and are in scope of ongoing revisions of quality guidelines on stability of drug substances and drug products (ICH Q1(R1))[4] and specifications (ICH Q6 (R1))[5]. However, common documentation standards for ATMP quality information are not yet established within the ICH framework, though the updates in the ICH M4Q (R2) revision [6] may address several aspects. In addition, efforts on a new guideline, ICH E23 [7] Considerations for the Use of Real-World Evidence (RWE) to Inform Regulatory Decision Making with a focus on Effectiveness of Medicines, will be valuable to the ATMP field.

At this time, the absence of international guidance on many considerations during the life cycle of an ATMP and the lack of harmonisation for ATMP regulatory expectations result in challenges to global drug development and regulatory decision making. The rapid evolution of new technologies in the ATMP field also makes it challenging to establish regulatory expectations, particularly given the emerging new types of ATMP products and manufacturing processes.

There is a wide variety of complexity across ATMPs, and special considerations often depend on the specific ATMP subclass. Notably, many regional guidelines focus on a specific subclass of ATMP products. While nomenclature and classification of ATMPs are not globally aligned, these are typically codified in regional laws and regulations and are out of scope of ICH.

For the purposes of the ICH CGTDG's work, the WHO framework [8] and associated terminology were applied. Applying the WHO definitions, ATMPs include four subclasses of medicinal products: (1) Gene therapy products, (2) cell therapy products, (3) tissue engineered products, and (4) combined ATMPs, and the WHO definitions of these ATMP subclasses are provided in the Glossary. Gene therapy products include both *in vivo* products that deliver therapeutic genes or correct genetic mutations directly in the patient cells (e.g., nucleic acid-based or viral vector-based) and *ex vivo* products where the recombinant gene is delivered to cells outside of the patient's body. The latter are often called *ex vivo* genetically modified cells, *ex vivo* gene therapies, or cell-based gene therapies (e.g., CAR T-cell products).

The nature of these products and their manufacturing processes can require alternative approaches (with scientific justification) from those established for traditional biotechnological and biological products. In addition, the unique considerations often differ between ATMP modalities (e.g., nucleic acid-based ATMPs versus cell-based ATMPs). While the principles of drug development generally apply to ATMPs, existing ICH guidelines are not always directly applicable and fit-for-purpose approaches may be justified. The CGTDG herein provides a strategic roadmap with specific recommendations for new ICH guidelines, revisions, or annexes to existing ICH guidelines to address the special circumstances for ATMPs, while adopting high level principles given their complexity, diversity, and evolving nature. The strategic roadmap is aligned with ongoing revisions of ICH guidelines, which include in their scope consideration for a broad range of ATMP modalities. Neither the recommendations in the strategic roadmap nor the high-level principles are to be understood as scientific guidance but instead may be the basis for future guidelines.

**REMIT OF THE CGTDG AND SCOPE OF CONSIDERATION**

The ICH Management Committee (MC) agreed (August 2023) to launch a cell and gene therapy discussion group (CGTDG) to serve as a technical discussion forum for issues related to ICH harmonization efforts in the ATMP field. The overall aim of the ICH CGTDG was to develop a strategic framework to address the future harmonisation needs for this emerging field, and to provide recommendations to the ICH MC to guide ICH activities to address the technological advancements in the ATMP field across the clinical, nonclinical, and quality disciplines. Given the scientific complexities and diverse array of CGT modalities, the CGTDG focused on therapeutic modalities of relatively high maturity where scientific and regulatory expertise have already been achieved, namely, *ex vivo* genetically modified cell-based products (e.g., CAR T-cell products) (both autologous and allogeneic) and *in vivo* viral vector-based gene therapy products (e.g., AAV vector-based products). The recommendations for these therapeutic modalities may be applicable to other ATMPs.

The objectives of the group were to drive alignment on high-level principles where baseline consensus could be achieved regarding the special considerations for ATMPs, and to develop a holistic roadmap based on prioritization, which was jointly established by regulators and industry, of areas of most need for harmonization with specific recommendations for new guideline development or revisions to existing guidelines. In accordance with the remit, the ICH CGTDG undertook a comprehensive assessment of the applicability of existing ICH guidance and generated a strategic roadmap, which is shown in the table below and considers ICH resource limitations for parallel development of guidelines as well as the evolving nature of ATMPs.

**POTENTIAL OPTIONS FOR ADDITIONAL GUIDANCE**

The following options were considered across ICH Quality (Q), Safety (S), Efficacy (E) and Multidisciplinary (M) guidance: Guideline revision, annex to existing guidance, or development of new guidelines. It is recommended that future guidelines and ATMP annexes address a broad range of ATMP products (i.e., not only those of relative maturity), and annexes include some redundance with information in the core guideline to enable the reader to fully understand the ATMP-specific recommendations. In addition, the use of training materials to illustrate the application of a guideline to ATMPs was considered. Several ATMP topics that were prioritized by the CGTDG and highlighted in the high-level principles section are currently being addressed by existing EWGs undergoing revised guideline development where CGT products are in scope (e.g., ICH Q1(R1) Stability Testing of Drug Substances and Drug Products; ICH Q6(R1) on Specifications: Test Procedures and Acceptance Criteria).

Provided in the table below are the CGTDG’s recommendations for specific key topics and how to address them within the ICH framework in the future. The list of recommendations reflects the prioritization for addressing these topics based on the criteria provided in Annex I.

**TABLE 1: STRATEGIC ROADMAP OF PRIORITIZED TOPICS WITH SPECIFIC RECOMMENDATIONS FOR HARMONISATION**

| Topic | Recommendation and Considerations: ***Problem statement, potential content/scope for EWG/IWG, type of modality(s) specifically in-scope, aspects of a Concept Paper***<br><br>☐ ***= Topic Endorsed/Ongoing*** |
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| Comparability<br>***(Endorsed)*** | *Recommendation:* *Comparability of Advanced Therapy Medicinal Products (ATMPs) Subject to Changes in Their Manufacturing Process (*Annex to ICH Q5E) (core guideline not to be opened for revision)<br><br>Expectations for comparability assessments are primarily addressed in ICH Q5E, which is suitable for well characterized biological products. However, the principles are difficult to strictly apply to ATMPs with greater complexity and variability and novel circumstances. There is a need for a broader risk-based approach that uses the totality of evidence to manage uncertainties and unique considerations. Refer to press release (21 May 2025) regarding ICH Assembly Meeting, Madrid, Spain under “New Areas of ICH Harmonisation” |
| Long-Term Follow-Up (LTFU) | *Recommendation:* New ICH E guideline on Long Term Follow up for ATMPs covering the following topics:<br>-Monitoring expectations during both clinical development and post-approval.<br><br>- Factors influencing the duration and methods of follow up including product characteristics (e.g. persistence, mechanism of action, shedding), patient demographics and clinical context and nature of the disease and potential delayed adverse events. The risk-based approach should also include an assessment of whether LTFU is needed.<br><br>- Detailed recommendations on what should be monitored including identification and assessment of delayed adverse events, severity and duration, evaluation of sustained therapeutic benefit and quality of life and monitoring for unintended integration or unintended gene editing. The unique biological and genetic mechanisms of action of ATMPs necessitate specialized monitoring approaches, particularly for unintended genomic alterations such as insertional mutagenesis or off-target gene editing. The burden of LTFU monitoring on the patient and healthcare system should, however, be considered in order to achieve a balance. If the patient burden is high, the dropout rates may increase and ultimately diminish the body of data collected and its corresponding value. |

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| | - Guidelines for systematic data collection, management and analysis to ensure data integrity and reliability, employing specialized data collection methods, including patient registries and electronic health records, to gather comprehensive long-term outcome data placing a greater emphasis on patient engagement and informed consent for ongoing monitoring, highlighting the importance of patient-reported outcomes.<br><br>Primarily addressed in ICH E8, E17 and E19; however, existing guidelines do not address LTFU requirements specific to ATMPs. |
| Development and manufacture of ATMP | *Recommendation:* Annex to ICH Q11 is recommended, particularly to harmonise control strategy and material quality expectations for ATMPs.<br><br>General Considerations:<br>Developing a robust control strategy can be uniquely challenging for some ATMPs due to the inherent variability of the starting material and limitations of analytical testing (e.g., limited amounts of material, method limitation).<br><br>Quality of raw and starting materials is a substantial issue that is multi-faceted. While various aspects are, in part, addressed in several ICH Q guidelines (e.g., Q5A, Q5B, Q5D, Q7, Q8, Q10, Q11), the lack of harmonized definitions of materials and associated regulatory requirements leads to different nomenclature for materials and complexities in filing of information in different regions.<br><br>Process development and validation/evaluation are partially covered by ICH Q8 and Q11. Due to ATMP specificities, there is a need for alternative approaches when "standard" development or validation approaches cannot be achieved including alignment on methodology for risk-based approaches. Use of platform approaches and technologies in the production of ATMPs should also be considered.<br><br>Considering the scope of ICH Q11, including topics such as Lifecycle Management (Chapter 9), Submission of manufacturing process development and related information in CTD format (Chapter 8) which may be required to be aligned with revised ICH M4Q(R2), or Illustrative examples (Chapter 10) could also be considered in an Annex to Q11. |

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| | This annex should provide ATMP-specific guidance for:<br><br>- Process development and validation/evaluation, e.g., discuss enhanced approach to development for ATMPs, address the inherent variability depending on the modality, and propose alternative approaches where appropriate.<br><br>- Starting and raw material: Clarify and consolidate regulatory expectations, moving beyond current regional differences to the extent possible. This includes aligning technical requirements for starting materials (e.g., quality criteria, viral safety aspects, traceability, transportation). For raw materials, the annex should detail general quality and safety requirements, particularly for those of human or animal origin, addressing varying grades of quality for all components, including genetic modification reagents, and adventitious agent concerns.<br><br>- Control strategy: recognizing the inherent variability of many ATMPs, especially autologous cell-based products, and the evolving understanding of optimal dosing and manufacturing processes, the annex should discuss a risk-based approach for establishing a robust control strategy, and where appropriate and in consideration of possible regional constraints, advise on the management of out-of-specification (OOS) batches.<br><br>- Build upon existing ICH guidance (e.g., M4Q, Q6, Q9, Q12) and international guidance where appropriate (e.g., PIC/S annex 2A). Consider providing illustrative examples including various subclasses of ATMPs. |
| Nonclinical considerations for ATMPs | *Recommendation:* New ICH S guideline on nonclinical evaluation of ATMPs that covers a range of topics (listed below).<br><br>Species selection (i.e. relevance of animal model):<br>Primarily addressed in ICH S6 for biotechnological products, with additional considerations for reproductive toxicology and safety pharmacology studies in ICH S5 and S7, respectively. Existing guidelines do not address specific attributes of many ATMP modalities, including the determination of species biological relevance due to differences in tissue tropism (e.g., for in vivo viral vector-based gene therapy products) or antigen expression and recognition (e.g., for CAR T-cell products), biodistribution, and immunogenicity (including preexisting immunity)). Harmonized guidance on |

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| | considerations in determining species biological relevance and on the number of toxicology species, rationale for selection (incorporating 3R principles of replacement, reduction, and refinement to minimise use of animals), use of alternative models (including nonstandard species and in vitro/in silico approaches), and use of surrogate products could be provided with a focus on ATMP-relevant aspects. The degree of personalisation of a product also adds to the complexity of ATMPs and may lead to alternative models being more relevant. Considerations for in vivo gene editing products should be addressed.<br><br>Nonclinical study duration and endpoints:<br>Primarily addressed in ICH S6 for biotechnology products, S9 for anticancer pharmaceuticals and S4 for medicinal products which are not covered by S6 or S9. Existing guidelines do not address specific attributes of many ATMP modalities, including the single dose administration limitation, the limited duration of treatment effect due to the development of immunogenicity, and species-specific pharmacology. Study durations and endpoints are largely unstandardized and considered on a case-by-case basis. Harmonized guidance to determine the appropriate study duration and endpoints based on ATMP pharmacology, biodistribution and PK/PD profiles could be provided.<br><br>Integration:<br>Integration, and the risk of insertional mutagenesis, is a unique attribute of ATMPs not addressed in existing ICH guidelines. Integration is discussed only in the context of germline transmission in the 2006 ICH consideration document, “General principles to address the risk of inadvertent germline integration of gene therapy vectors”. Harmonized guidance to evaluate the risk of insertional mutagenesis, including the use of insertion site analyses (e.g., for *in vivo* viral vector-based gene therapies; in vivo gene editing products, ex vivo genetically modified cells), as well as to characterize on-target and off-target effects of gene editing products, including translocations and structural variants, could be provided.<br><br>Carcinogenicity and tumorigenicity studies:<br>Primarily addressed in ICH S1, with considerations for biotechnology products in ICH S6 and for anticancer pharmaceuticals in ICH S9. Existing guidelines do not address specific attributes of many ATMP modalities (e.g., insertional oncogenesis potential) and are generally not considered applicable to ATMPs, resulting in the absence of harmonized guidance on factors triggering the need for carcinogenicity/tumorigenicity studies or suitable experiments to characterize the |

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| | carcinogenicity/tumorigenicity of ATMP products. This lack of harmonized guidance may lead to divergence during global development and regulatory review. Harmonized considerations on the need and type of studies could be provided.<br><br><u>Germline Transmission:</u><br>Primarily addressed in ICH S12 and the 2006 ICH consideration document, "General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors". Guidance available in S12 addresses biodistribution to gonadal tissue and its ability to inform the risk of germline transmission. However, assessment of germline integration of gene therapy products is outside the scope of S12. The ICH consideration document provides recommendations for patient monitoring if distribution to gonads is detected. There may be an opportunity to update/codify recommendations with a new ICH guideline that goes beyond current guidance on distribution to gonadal tissue and provides guidance on evaluation of potential germline integration.<br><br><u>Development and reproductive toxicity (DART) studies:</u><br>Primarily addressed in ICH S5, with considerations for biotechnology products in ICH S6 and for anticancer pharmaceuticals in ICH S9. Existing guidelines do not address specific attributes of ATMPs. There is no harmonized guidance on the need for or timing of DART studies for gene therapy vectors which has led to divergence in regulatory views across ICH regions. The potential for inadvertent germline transmission is a unique attribute of ATMPs that differs significantly across ATMP modalities. As discussed in ICH S12, an ATMP's potential for germline transmission may be addressable with biodistribution studies that characterize the extent of distribution to ovaries and testes, and more specifically, to oocytes and spermatocytes within these tissues. Harmonized guidance on the need and timing of additional DART studies beyond characterization of germ cell distribution could be provided.<br><br><u>Risk-based approach to nonclinical studies for ATMPs:</u><br>It would be valuable for the new S guideline to provide guidance on risk-based approaches, and to address the use and assessment of data from nonclinical studies from other but similar products. This can include evaluation of prior knowledge from the scientific literature and/or similar products along with their relevance and how to identify and address potential gaps. |

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| Considerations for early phase/exploratory clinical trials evaluating ATMPs | *Recommendation:* Annex to ICH E8. The annex should include the following topics:<br><br>•**Approaches to bridging non-clinical findings to clinical application**: While ICH E8 provides a framework for the comprehensive evaluation of preclinical data relevance, addresses variability in study designs, and emphasizes the integration of mechanistic insights to inform clinical relevance, specific guidance tailored to the unique challenges and characteristics of ATMPs is needed. For example, this guidance may address the design and conduct of clinical studies (e.g. small, open-label, non-randomized, single-arm trials) and the incorporation of clinical prior knowledge based on natural history exercises.<br><br>•**Guidance on the design of studies that account for single-dose administration**: While ICH E8 mentions long-term effects, it does not specifically address the challenges associated with single-dose administration of ATMPs. Guidance on how to design studies that effectively capture the long-term safety and efficacy of a single administration, including appropriate follow-up durations and methodologies, would be beneficial. The current guidance does not sufficiently address the need for specific types of clinical endpoints that could be more relevant to ATMPs.<br><br>•**Patient selection given the disease characteristics, genetic variability, patient exclusion**: ICH E8 mentions the importance of considering patient populations but further guidance is needed to account for variability in patient responses due to genetic factors, prior treatments, and disease heterogeneity, especially since ATMPs may be tailored to individual patients.<br><br>•**Dose selection and the use of prior knowledge**: ATMPs can exhibit non-linear pharmacodynamics. The guidance should address how to determine the optimal dose which may not follow traditional dose-response relationships. In addition, recommendations may include the following 1) how to evaluate the sustained efficacy and safety of a single administration over time; 2) assess the relevance of prior knowledge, and 3) incorporate patient genetic and phenotypic variability.<br><br>•**Immunogenicity considerations**: ICH E8 addresses immunogenicity as a general consideration in the context of clinical trials, primarily focusing on the need to assess the safety and efficacy of medicinal products, including the potential for immune responses that could affect therapeutic outcomes. However, the immunogenic potential of ATMPs can vary significantly based on the type of |

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| | product (e.g., gene therapy, cell therapy) and its components (e.g., viral vectors, therapeutic proteins). Factors such as the source of the therapeutic material (autologous vs. allogeneic), the presence of non-human proteins, and the method of delivery can influence immunogenicity and therefore, further guidance is needed.<br><br>•**Pediatric specific considerations**: Primarily addressed in ICH E11(R1) and E11A, general principles apply to ATMPs, potential specific considerations for pediatric development to be included in annex to E8.<br><br>•**Prospect of benefit**: Sufficient prospect of clinical benefit is required to justify the risks of exposing the pediatric population to an investigational ATMP product, as for all medicinal products. Guidance should include considerations for ensuring the prospect of benefit when ATMPs are administered to pediatric populations.<br><br>•**Dose extrapolation and safety data**: For certain ATMPs (e.g., AAV vector-based gene therapy products), pediatric patients may require a higher per kg dosing regimen, and there may be a need to monitor key safety events early on individually or in very small cohorts. This is currently addressed using a case-by-case approach depending on the type of therapeutic.<br><br>•**The durability of response** to ATMPs depending on target tissue: Though not specific to the pediatric population only, the guidance should include considerations for evaluating tissue-specific distribution patterns and persistence, recognizing that the pharmacokinetics or cellular kinetics may vary significantly across different tissues.<br><br>• Clarifications that distinguish among ATMP modalities could be provided in illustrative examples or training materials. |
| Viral safety | <u>*Recommendation:*</u> Annex to ICH Q5A(R2) to address cell-based ATMPs.<br><br>An annex for cell-based ATMPs was not developed because they were out of scope of the ICH Q5A (R2) revision, which included products amendable to viral clearance without a negative effect on the product (e.g., viral vector-based gene therapy products). Since there is no technology established yet for virus clearance or inactivation in cell-based medicinal products, these were out of scope of ICH |

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| | Q5A (R2) though some of the general principles may be used as appropriate. Viral safety of cell-based medicinal products may need to be ensured through control of starting or raw materials and aseptic manufacturing processes. There is a potential opportunity to address some aspects of virus safety risks of cell-based medicinal products in an ICH Q11 annex in sections related to starting and raw materials. |
| Assay validation | *Recommendation:* Training materials to include case studies of unconventional analytical methods for ATMPs to further clarify development and validation expectations, as appropriate.<br><br>ICH Q2 and Q14 are the primary guidelines; while the guidelines mostly apply, some unconventional assays would benefit from further examples. |

*Regarding the relative timing of the guidelines, the new ICH S guideline (Nonclinical considerations for ATMPs) should be initiated before the start of efforts on the annex to ICH E8, Considerations for early phase/exploratory clinical trials evaluating ATMPs, so that the scope of nonclinical considerations are defined first.

## HIGH-LEVEL PRINCIPLES

High-level principles were adopted in recognition of the complexity, diversity, and evolving nature of ATMPs, which limit the applicability of current ICH guidance at this stage. These are key areas where ATMPs differ from traditional biotechnological products and alternative approaches or interdisciplinary considerations may be needed. These high-level principles are not to be understood as scientific guidance but instead may provide underlying reasons for the need for new guidelines or revisions to existing guidelines or may be the basis for future guidance. ATMPs are a broad class of complex biological products with a wide range of characteristics. Risk-based approaches are applicable throughout the life cycle of ATMPs and may justify alternative approaches to the usual quality, non-clinical, and clinical requirements. The complexity of these products and the difficulty to relate a multitude of product quality attributes to clinical outcomes, along with the limited manufacturing and clinical experience, can pose more risks, though urgent medical needs may still result in acceptable patient benefit-risk balance.

Although many ATMPs are developed to treat rare hereditary diseases and/or pediatric patients, these considerations are *not* reiterated in this document since they are also applicable to other classes of medicinal products. For some ATMPs, the amount of time needed to demonstrate therapeutic effectiveness is quite long (e.g., several years when a hereditary disease progresses slowly). In some cases, an

ATMP can be administered to a patient only once, for example, due to the patient's immune response, necessary concomitant treatment, or other factors, and this exposure may preclude the patient from subsequently receiving similar medicinal products in the future.

**Interdisciplinary considerations for ATMPs**

For ATMPs, several aspects of their manufacturing and controls have direct clinical implications. For example, the end-to-end turnaround time for manufacturing and testing of autologous cell-based products needs to be minimized since the patient awaits their treatment; it is therefore desirable to have proximity of manufacturing to clinical sites, and this is a key driver for decentralized manufacturing strategies.

There are several interdisciplinary considerations for *ex vivo* genetically modified cells. For example, a CAR T-cell product is an immune cell that has undergone genetic modification to express a chimeric antigen receptor (CAR). One of the potential challenges is the induction of humoral and/or cellular immune response in patients to the CAR construct if this is of non-human origin. When the CAR T-cell product is autologous (i.e., patient-derived starting cells), immune rejection is minimized, though patients can develop antibodies to lipid formulations even when non-viral genetic modification methods are used. However, when the CAR T-cell product is allogeneic (i.e., donor-derived starting cells) then a strategy is needed to avoid immune rejection (e.g., graft-vs-host-disease (GvHD); host-vs-graft disease (HvGD)). The procedures for cell procurement (e.g., apheresis) can be burdensome for patients. In addition to the difficulties in collecting and handling source materials, there is inherent variability of starting cells and tissues for production of cell-based ATMPs. Traceability (e.g., chain of custody/identity) between the donor and recipient is crucial and can be logistically burdensome. In addition, ATMPs may require special storage conditions, and their transportation and handling requirements may pose challenges in clinical settings.

In cases where an ATMP cannot be cryopreserved and consequently has a short shelf life (e.g., several hours) there is insufficient time to complete all release testing (e.g., conventional sterility test) prior to administration to the patient; alternative approaches such as rapid microbial test methods or testing of intermediates may be necessary to ensure product quality and enable administration to patients in a timely manner.

For individualized (i.e., patient-specific) ATMPs (e.g., autologous CAR T-cell products), there are clinical implications when manufacturing and/or release testing failures occur, since they result in treatment deprivation for patients who have already undergone the procedure for acquiring cells (e.g., apheresis); this necessitates communication directly between the manufacturer and treating physician. There are both patient-specific and product-specific aspects of product quality for individualized ATMPs. For autologous cell-based products, the cellular starting material is derived from the patient and the health of the patient influences the quality of their batch (e.g., viability of cells). This is a consideration when additional disease indications involve a different patient population with potential differences in health status. For autologous CAR T-cell products, the impact of product variability on clinical response is often monitored during clinical development and post-approval, and is generally needed over the lifecycle of the product. The use of real-world evidence (RWE) can be considered.

Although the batch size for patient-specific (individualised) ATMPs is inherently small (e.g. autologous CAR T-cell product), one batch is typically manufactured for each patient and this ultimately results in a large number of batches (relative to off-the-shelf products for rare diseases where there may be only few batches). Patient-to-patient variability is inherent and is reflected in the product quality.

Measuring the strength of an ATMP is not always straightforward, and this can become an issue for properly defining the dose in nonclinical and clinical studies. For example, the quantity of a viral vector-based gene therapy is typically measured in vector genomes/milliliter (vg/ml). The amount of *ex vivo* genetically modified cells is often defined by the number of viable cells that have successfully been genetically modified. Changes in the analytical methods for measuring quantity and/or changes in how the amount of active substance is defined will impact the reported dose.

**Quality considerations**:

**Product complexity and variability**

While the extent of variability depends on the type of ATMP, there is generally a greater degree of complexity for ATMPs than traditional biotechnological products, and the product quality attributes are not always well understood. Deciphering which aspects of product quality are impactful to safety and/or efficacy and establishing acceptable ranges can be challenging. The aforementioned inherent variability of the starting cellular materials for manufacture of cell-based products (both autologous and allogeneic), also contributes to variability in the final product batches.

For viral vector-based gene therapy products, the therapeutic gene of interest is packaged inside the viral capsid, which is generally composed of viral proteins that assemble to form a protective shell around the nucleic acid payload. Once assembled, the viral capsid functions to transport and deliver the therapeutic gene to the intended target cells where it can be expressed. There is inherent heterogeneity in the viral capsids and there may be process-related impurities associated with or incorporated into the final product.

When the ATMP is composed of living cells, it is inherently dynamic due to metabolic activity, cell division, apoptosis, and other factors. The identity of the cells is typically determined with genotypic and/or phenotypic markers (e.g., cell surface markers), and the proportion of cells with these markers is usually an indication of the intended cell population. The cell population generally includes some non-viable cells and unintended cell populations which are considered impurities.

Given the specialised nature of ATMPs, and depending on the type and extent of non-compliance, it is possible in some regions that after a careful risk and benefit analysis, the administration of an out-of-specification autologous CAR T-cell product batch is considered to be in the best interest of the patient. In these cases, a collaborative risk-benefit assessment is conducted with the treating physician according to regional regulations. While this practice is quite exceptional in the broader context of all medicinal products, it occurs more commonly for autologous cell-based ATMPs (often due to differences in patient populations in clinical studies versus patients receiving the marketed product). It is important to note that these cases involve test results outside of the acceptance criteria for specific quality attributes (e.g., viability of cells) rather than the entire specification. Additional implications (e.g., reimbursement) depend on whether the ATMP is an investigational or marketed product.

**Limited amounts of product**

ATMPs are often produced in much smaller amounts than traditional biotechnological products. The limited amount of ATMP product can constrain all aspects of development, including analytical method development, product characterisation, release testing, stability testing, and comparability assessments, as well as retention samples and import testing. The limitations of available product may also cause constraints on nonclinical and clinical studies.

Typically, ATMPs are manufactured in limited quantities with small batch sizes, due to many factors, such as limited starting material (e.g., for autologous products), manufacturing process complexity (including scale up and scale out), high cost, manual operations, and overall time required to manufacture (e.g., several months in some cases). Relying on release testing of an intermediate or use of in-process controls may be an alternative approach to control strategy to conserve product. Nondestructive analytical methods as well as those requiring low sample volumes can also help conserve product for other uses. Limited availability of patient-derived cells for autologous cell-based ATMP production may require the use of surrogate materials from healthy donors for comparability assessments, characterisation purposes, method validation, and support of process validation and stability, provided they are representative.

Many ATMPs are developed for rare diseases, and few batches may provide sufficient material for clinical development and market supply. When the number of manufactured ATMP batches is quite small, it can become difficult to assess manufacturing consistency, and this may become an issue for process characterization and validation as well as comparability assessments. Small numbers of batches affect the data set available when setting specifications and can impact stability study design. If an off-the-shelf ATMP (e.g., AAV vector-based gene therapy product) needs to be administered in a relatively high dose to be effective, then a large portion of a given batch may be administered to only a few patients, resulting in a limited number of patients exposed to a product batch with its particular range of product quality attributes.

**Lack of defined drug substance**

In some cases, ATMP production is a continuous process with no distinct drug substance. While this is not unique to ATMPs, when the manufacturing process is an uninterrupted stream without a defined drug substance, there are implications for release testing and specifications, stability testing, and the overall control system.

**Quality of source/incoming materials**

Unlike most pharmaceuticals, ATMPs are often manufactured using substances of human origin, which can include starting cellular material and/or excipients (e.g., human plasma). These pose a risk of transmission of blood-borne infectious agents to patients as well as manufacturing personnel.

Traceability between the patient and the source of cells/tissues and other biologically derived materials used in manufacturing is important for ATMPs. Error-free chain of identity/custody is crucial for autologous products since batch mix-ups will have serious safety consequences for patients.

There are many biologically derived raw and starting materials used in ATMP manufacturing. Although they introduce the risk of adventitious agents, they cannot always be readily replaced with chemically derived components. Generally, biologically derived materials are complex, may not be well defined, and can display low batch-to-batch consistency. The impact of materials on the quality of the ATMP drug substance or drug product can be substantial, since cells can be sensitive to variations in the quality and composition of materials (especially those used in culture medium).

It is important for manufacturers to consider the importance of the quality of incoming materials (i.e., raw materials and starting materials) and establish phase-appropriate specifications, and account for risks to the overall control strategy. Starting materials that are considered critical due to their impact on product quality (e.g., viral vector for *ex vivo* genetic modification of cells) may need to be documented with the same level of information as an active substance.

When the starting cells for manufacture of cell-based ATMPs are derived from a patient or donor (e.g., apheresis material), they are typically procured in blood/tissue establishments under Good Tissue Practice (GTP) compliance requirements and regional donor eligibility requirements need to be satisfied, as appropriate. The manner in which the cells are collected, handled, cryopreserved (if applicable), stored, and transported can affect the final product quality. Tissue establishments must comply with local legal requirements; their certification requirements are outside of ICH scope, though details of traceability and GTP compliance may need to be provided to local health authorities.

Although autologous cell-based products do not pose a risk of transmission of infectious disease from donor to recipient, tests for viral adventitious agents during donor eligibility assessment are generally required in all regions, and may be useful for other reasons, such as ensuring proper protection for manufacturing personnel and preventing cross contamination. In contrast, allogeneic cell-based products do pose a risk of transmission of infectious disease from donor to recipient and proper donor eligibility screening and testing are essential.

The standards and procedures utilized for donor selection are established regionally/nationally and include emerging pathogens, which are ultimately considered in the overall control strategy. In some countries, donor eligibility requirements are set in national laws for transplantation purposes and are outside of pharmaceutical regulatory frameworks or may be set in national standards for biological raw materials. While many infectious agent testing requirements are common across regions, emerging pathogens tend to differ between regions and test method certifications differ between regions. Depending on how human-derived materials are used in ATMP production, manufacturers may need to implement fragmented supply chains that procure materials regionally to meet local requirements.

**Analytical method limitations**

Improvement of the quality control of ATMPs will depend on advances in analytical technologies. In general, the analytical methods for characterization, release, and stability testing of ATMPs are often variable. For cell-based ATMPs in particular, innovative or unconventional analytical methods, which may be qualitative or semi-quantitative in nature and which might lack robustness and standardisation, are often employed. Taken together, these factors pose challenges to the setting of specifications and acceptance criteria for release and stability.

While conventional methods are preferred, they are frequently not feasible with ATMPs. For example, rapid microbiological tests that consume small amounts of material and take less time than traditional tests are often necessary for cell-based ATMPs and are available in certain pharmacopoeias.

The mechanisms of action of ATMPs can be complex and this poses challenges to developing a reliable potency assay that reflects the biological activity contributing to clinical efficacy. A multifaceted approach may be required, including assessment of gene transfer efficiency, determination of the therapeutic sequence expression level or its direct activity, and measurement of the therapeutic sequence or product functional activity. The clinical phase should also be considered in the development of an appropriate potency assay.

**Reference materials/standards**

Several initiatives are underway to establish reference standards for ATMPs, though such standards are often unavailable and in-house reference material generally needs to be prepared from batches representative of production and clinical materials. In addition, reference standards for ATMPs may be produced in limited amounts, which often restricts their use and necessitates frequent preparation. For individualised (i.e., patient-specific) ATMPs, reference materials cannot be fully representative of every patient batch; nevertheless, representative reference materials may cover a range of patient-specific product quality attributes and can be used to ensure that analytical methods perform properly.

**Stability considerations**

Given the diversity of ATMP products, the approach to stability studies will be based on the product type and its manufacturing process. Accelerated and stress stability studies may be helpful for understanding the degradation profiles of some ATMPs and support shelf-life extensions and comparability exercises. However, there may be complex degradation properties of some ATMPs (e.g., cell-based products), and accelerated stability conditions may not be informative of the degradation pathways that occur during storage. When accelerated conditions provide limited information, the shelf life of an ATMP can be based on real-time data under the intended storage condition. When there is limited availability of material, then prior knowledge from similar products and/or data from representative development batches and from predictive stability modeling may be supportive. In specific circumstances where no measurable degradation takes place in the time frame of storage (e.g., cells stored below -130°C since there is no liquid water present in the product and the cells can be stable for many years), the testing frequency of a typical stability protocol may not be relevant.

Many ATMPs are stored at very low temperatures and/or in unusual container closure systems, which may have implications for labeling primary containers. For cryopreserved cell-based products, it's important to verify the potency and viability of cells after thawing, or provide bridging data that support consistency of pre- and post-cryopreservation product so that the correct number of viable cells and corresponding volume of drug product is infused.

While stability of autologous cell-based ATMPs would ideally be obtained from patient-derived material, due to limited availability of patient material there can be ethical and/or logistical considerations affecting the use of patient material for stability studies; representative surrogate batches manufactured from healthy donor cells might be used in demonstration of stability studies. Cell-based ATMPs may also be sensitive to physical forces, which might occur during shipping and handling.

The limitations in suitable analytical techniques to identify stability-indicating product quality attributes and to understand complex degradation pathways are considerations when predicting the shelf-life of an ATMP. Product-related impurities typically accumulate during storage or degradation of a medicinal product, and there may be a need for orthogonal methods to measure impurities and degraded materials in ATMP products.

The complicated modes of action of ATMPs, together with the inherent variability of patient-specific products and highly complex product types contribute to the challenges of assessing stability. For viral vector-based gene therapy products, the total viral particle number and viral genome titer are important to preserve, as are infectious units and potency.

Given the important role of starting materials (e.g., cellular starting material and genetic modification tools), the stability of these needs also to be evaluated. The stability of viral banks used in production of *ex vivo* genetically modified cells or as *in vivo* gene therapy products also need to be evaluated for purposes of manufacturing robustness and consistency.

Refer to ICH Q1 (R1) with an annex on ATMPs and supporting annex on stability modeling for recommendations for assessing the stability of drug substance, intermediates, and drug products, as well as starting materials, of ATMPs.

**Comparability assessments**

The complexity of ATMPs, the inherent variability of patient-specific cellular starting materials adding to product variability, and limited characterization pose challenges to demonstrating comparability when manufacturing changes are made. In addition, ATMP manufacturing processes undergo frequent changes due to rapid evolution of technologies and site transfers.

Comparability exercises are essential throughout the lifecycle of ATMPs including during clinical development and post-approval. The ability to show that process changes have no adverse impact on the quality, safety and efficacy of a medicinal product is essential for maintaining continuity. However, the principles for assessing comparability established in ICH Q5E are suitable for well characterized biological products but can be difficult to directly apply to ATMPs. It may not be feasible to comprehensively characterize many types of ATMPs at the molecular level (e.g., cell-based ATMPs). A strict interpretation of traditional approaches to demonstrating comparability may be impractical, uninformative, or even prohibitive to ATMP development and market approval. Alternative approaches are often needed and may include the use of surrogate starting materials for autologous cell-based products, as well as split manufacturing. When changes are made in raw or starting materials for ATMP manufacturing, the comparability of the materials may need to be demonstrated (with confirmation at the drug substance and/or drug product level).

The importance of demonstrating representativeness of post-change product to maintain continuity of development and/or supply cannot be overstated. In early development, representativeness of material used in preclinical and early clinical studies is important. Manufacturing changes during or after late-stage or confirmatory clinical trials may impact the ability to combine clinical data derived from pre-change and post-change product.

**Additional information about the relatively mature ATMP modalities that were the focus of the CGTDG**

***In vivo* viral vector-based gene therapy products**

Minimally or non-integrating viral vectors primarily persist in episomal form after transduction of target cells. For *in vivo* viral vector-based gene therapy products (e.g., adeno-associated virus (AAV) vector-based), manufacturing generally involves master cell banks and plasmids, or master virus banks (e.g. adenovirus vector-based) as starting materials. When helper viruses are used during manufacturing, their design, construction, production, and banking systems have an important role. During AAV assembly, a heterogeneous mixture of full, partially full, and empty capsids are produced, and these should be quantified throughout clinical development.

For conditionally replicating or replication-deficient viral vectors (e.g., AAV-based gene therapy products), there is potential contamination of the production cell line by wildtype, helper, or hybrid viruses that could lead to formation of replication competent viruses, which are known potential impurities. The infectivity potential and the titer of the viral vector are important, as is the presence of inserted or deleted genetic sequences and the potential for oncogenic and/or tumorigenic sequences.

For non-enveloped viral vector-based gene therapy products, certain process-related impurities (e.g., residual host cell-derived-DNA) can become incorporated into viral capsids and thus become part of product-related impurities that are more difficult to remove than process-related impurities, and may be immunogenic or lack the intended activity and thus may reduce overall effectiveness of the product. For some vectors, a relatively small percentage of full viral particles are infectious. In addition, viral capsids may aggregate.

The biological properties include the serotype of the vector, genetic modification of the vector (if any, such as to reduce immunogenicity), replication competency, tissue tropism, tissue specificity, and the intended result of the genetic modification accomplished by the gene therapy (e.g., introduction of functional copy of a gene). The mechanism of action is complex and often not fully defined, depending on the particular product and intended action of the encoded therapeutic gene. Potency measurements often include infectivity/transduction efficiency along with expression level of the therapeutic gene and the biological activity.

For AAV vector-based gene therapies, since the recombinant viral vectors are derived from natural AAV serotypes, there is pre-existing immunity. There may be differences in pre-existing immunity between different regions of the world based on environmental exposure. Potential patients may need to be screened prior to administration of the product (e.g., systemic administration). Once treated, the immune responses in patients involve adaptive humoral and T-cell mediated mechanisms and generally preclude subsequent doses as well as treatment with similar viral –vector-based products. In addition, there may be immune responses against the encoded therapeutic gene.

***Ex vivo* genetically modified cells**

For cell-based ATMPs, the final product is typically a heterogenous mixture of cell types that includes the therapeutic cells. The extent of different cell populations may have an overall impact on the product's safety and efficacy. The complexity and properties of *ex vivo* genetically modified cells and their manufacturing processes pose many new challenges in quality, nonclinical, and clinical. The therapeutic cells (e.g., CAR T-cell products) and the cellular starting materials are inherently variable. The active substance is composed of genetically modified cells. Genetic modification technologies are rapidly evolving and can include integrating viral vectors (e.g., lentiviral vectors) or genome editing.

The unmodified starting cells and the genetic modification tools (e.g., viral or non-viral vectors; guide RNA; mRNA expressing the modifying enzyme; modifying enzyme) are important. The transduction efficiency and the vector copy number per transduced cell are often characterized. When the cells are modified with integrating vectors, integration site characterization is of interest, and there is potential for large inversions, deletions, duplications, or chromosomal rearrangements. Homogeneity and genetic stability are of interest. When the cells are derived using genome editing tools, editing efficiency and on-target and off-target editing are important to understand.

Non-traditional analytical methods are often necessary for cell-based products. Variability in the assays and between analytical run sessions can pose a challenge to the usual expectations for analytical method validation and method transfer, as well as establishing specifications and shelf life and assessing comparability. Characterization may also involve proteomic, genomic, transcriptomic, or metabolomic analyses, for example, which may provide more holistic, albeit qualitative or semi-quantitative results. Appearance tests for cell-based products are complicated by the presence of the cells and inherent cellular debris, along with primary containers (e.g. infusion bags) that may make the detection of particulates challenging.

It is not possible to sterilize cell-based products by filtration, therefore, their overall sterility assurance strategy needs to focus on steps upstream of the final product. This places an emphasis on ensuring the purity of incoming raw and starting materials and maintaining aseptic conditions during manufacturing. In addition, sterility testing of the final cell-based product may be constrained by the limited amount and/or shelf life of the product.

For *ex vivo* genetically modified cells, the biological properties may depend on the origin of starting cells (e.g., apheresis material) and the technologies through which the product is generated (e.g., lentiviral vector). The biological activity of genetically modified T-cells (e.g., CAR T-cell products) depends on several factors, including the following: cell viability; number of vector copies per cell; transduction efficiency; CAR transgene expression; ability to secrete trophic factors; and the modified T-cells' cytotoxic activity, which together provide assurance of potency of the product batch.

**Genetically modified organism environmental risk assessments (GMO ERA)**

While environmental risk assessments (ERA) are generally applied to pharmaceuticals, the ATMP field is particularly impacted since many of these products are considered genetically modified organisms (GMO). GMO ERA are conducted to evaluate the potential impact of GMO release into the environment, and the requirements are generally defined in national environmental and/or agricultural laws, which are outside the scope of pharmaceutical regulatory frameworks, including ICH. There can be regional exemptions from GMO ERA requirements for ATMPs that are not capable of replication in the patient or in the environment. Navigation of GMO ERA can be time consuming for ATMP sponsors if there are not regional exemptions. For *in vivo* viral vector-based gene therapies, the risk of replication is a factor; vector shedding studies may inform the risk to healthcare providers and family members (e.g., also including seroconversion), as well as the environment.[9]

**Nonclinical considerations**

The nonclinical development approach for ATMPs may be significantly different from that of other medicinal products. Due to their complexity and potential long-term effects, a substantial portion of the nonclinical data is typically required prior to the first human exposure, particularly for *in vivo* gene therapy products. However, depending on the product type and risk profile, some nonclinical studies may continue in parallel with early clinical development.

There are often limitations of animal models for ATMP development. Differences between animals and humans (e.g., in terms of biodistribution, engraftment, differentiation, immunogenicity, and absence of human antigens) may limit the translatability of pharmacology and toxicology assessments, including their dose-dependence, to clinical outcomes. In some cases, suitable animal models may not exist due to lack of biological or pharmacological relevance of the ATMP in animals. In vitro and/or *in silico* modeling approaches may provide supportive information to address the limitations of animal models, and prior knowledge from similar products may also provide supportive information. In addition, depending on the product characteristics, evaluations of absorption, distribution, metabolism and excretion (ADME) that comprise conventional nonclinical pharmacokinetic assessments may not be feasible or relevant for some types of investigational ATMPs. For cell-based ATMPs the concept of "pharmacokinetics" is often replaced by "cellular kinetics" (CK) to emphasize the different kinetics of living cells compared to small and large molecule drugs. In some cases, it may not be feasible to conduct a nonclinical study in compliance with GLP standards. Repeat dose nonclinical studies may not be relevant or feasible for certain ATMPs (e.g., those intended for or limited to one-time administration to patients). Also, safety pharmacology studies may not be required if adequately justified. Standard genotoxicity studies may not be appropriate for ATMPs, though certain impurities or components of a gene therapy delivery system might pose genotoxic concerns.

With their genetic components, a unique aspect of ATMPs is the potential for unintended and durable genomic perturbations, including off-target integration and insertional mutagenesis, which may lead to oncogenesis. The risk profile varies depending on the integration potential and mechanism of the ATMP, such as viral vector-mediated gene transfer or the use of genome editing tools (e.g., CRISPR/Cas9). In the case of gene editing, additional concerns arise from unintended on-target as well as off-target genome alterations (e.g., large deletions, rearrangements) as well as transcriptomic perturbations. It may be valuable to test for these events early in development; such tests may be needed for gene therapy products that are considered integrating as well as those that are considered non- or minimally integrating, though prior knowledge should be applied appropriately. The potential for germline effects also arise as a concern if ATMP distribution to germline cells is detected. [1], [10]

The unique properties of ATMPs may require a multidisciplinary approach for better characterisation due to the limitations these properties can place on the utility of nonclinical studies. For example, there are clinical considerations on first in human studies (including dosing and PK/PD) and LTFU to address the limitations of animal model relevance and study duration and endpoints, and to supplement the nonclinical characterisation of the risk of integration, tumorigenicity, carcinogenicity, and germline transmission. In addition, there are quality considerations for characterisation to supplement the nonclinical characterisation of potential integration and tumorigenicity and carcinogenicity, as well as on representativeness of surrogate products, if used, with the investigational medicinal product.

**Clinical considerations**

The clinical development of ATMPs adheres to the same overarching principles for establishing safety and efficacy as other medicinal products, though the clinical trial phases are not usually as straight forward as they generally are for traditional products. They tend to proceed in ‘exploratory’ and ‘confirmatory’ stages rather than the conventional Phase I, II, and III studies. While this is also a general trend in drug development, an ATMP-specific feature is, for example, the patient-specific genetic intervention approach where there is a single patient with a unique genetic error that is targeted in a 1:1 manner. The facilitation of multi-regional clinical trials is important for ATMPs since many of these products are developed for the treatment of rare diseases with low global prevalence.

There are often limitations in the informativeness of nonclinical data for starting dose selection, biodistribution, on- and off-target effects, and tumorigenicity. Thus, there is often greater uncertainty in dose selection for FIH studies, particularly when relevant animal models and traditional pharmacokinetic and pharmacodynamic models are not available. Furthermore, the one-time administration of many ATMPs puts greater emphasis on the prospect of benefit at all doses evaluated.

In general, there is complexity in dose selection for ATMPs and dose considerations differ widely among ATMP modalities. The underlying disease, the stage of disease, and the desire to quickly obtain an efficacious dose in diseases without other treatment options, as well as the possibility that re-administration may not be possible, are factors to be considered. For example, early-stage patients with less disease progression may require lower doses while advanced-stage patients with greater disease burden may need higher doses to achieve therapeutic effectiveness, though this may increase the risk of adverse events.

The administration of ATMPs to patients can result in innate and/or adaptive immune responses which may be unwanted or detrimental, and animal models may not reliably predict immunogenicity. For *in vivo* viral vector-based gene therapy products, unwanted immune responses to the viral vector or the therapeutic gene should be considered. In addition, pre-existing immunity to the ATMP can affect patient population selection and influence future treatment options (e.g., in the case of AAV vector-based gene therapy products). Tests (e.g., *in vitro* diagnostics, companion diagnostics) can play an important role, such as determining if a patient should be excluded from treatment with certain ATMP products due, for example, to pre-existing immunity to specific AAV serotypes; a phase- appropriate approach is generally taken to validation of these tests.

Clinical safety considerations for ATMPs are sometimes different from other medicinal products and can include delayed adverse events, hence the need for long-term follow up monitoring. These may have implications for the selection of the waiting period between staggered administrations of an investigational ATMP. Due to the nature of certain ATMP products, studies in healthy volunteers are not always feasible (e.g., gene replacement in a healthy volunteer with a functional gene) or ethical (e.g., irreversible genetic modification). In certain situations, conducting a standard randomized, controlled trial may not be feasible or ethical; in such cases, single-arm trials (SAT) may need to be considered, acknowledging their inherent limitations including challenges with clinical endpoints without established regulatory acceptance or a well known natural disease course.

Diseases treated by ATMPs often do not have well described natural history, and information on prognostic baseline characteristics is lacking, unless there are well defined patient registries available for the disease condition. Together with the unique mechanisms of action and often long-lasting effects of ATMPs, these factors can complicate the interpretation of dose selection, treatment outcomes, and demonstration of efficacy. Furthermore, there may be a lack of accepted clinical endpoints, especially intermediate endpoints without established surrogacy for patient benefit. In some cases, the wide range of symptoms and severity levels may impact the assessment of treatment effect, as it may manifest differently across individuals with varying disease manifestations moreso than seen with traditional medicines.

In contrast to traditional biotechnological products, there may be lifelong duration of exposure for some ATMPs. In some cases, the intended clinical outcome can be observed only after a long follow up (e.g., slowly progressing disease). Generally, there may be uncertainty about the persistence of the ATMP's effect when there is a lack of understanding about the mechanisms of maintenance in human cells, or ability of a cell-based ATMP to persist. There can also be risk of delayed adverse events, such as tumorigenicity or carcinogenicity with ATMPs. For example, genomic integration-derived carcinogenic events may occur, or tumors can be derived from aberrant proliferation of non-genetically modified cells.

There is often a need for long-term follow-up (LTFU) of safety and efficacy due to prolonged biological activity of the ATMP and/or persistence of cell-based products. LTFU involves special considerations for ATMPs and balances the importance of monitoring safety and efficacy outcomes (including durability of patient response) with the overall burden that the monitoring has on healthcare systems, industry, and patients who receive these therapeutics. Patient discontinuation/dropout and the natural history of disease as patients age can affect the identification of adverse events causally linked to ATMPs.

Short- and long-term safety considerations become essential data in early development of ATMPs due to several novel aspects. For example, early-stage clinical studies may serve as confirmatory or pivotal trials and thus there is a need for well-planned studies and LTFU to address the limited safety database.

The patient's journey may be long and arduous for treatment with some ATMPs. Treatment often involves a complex and prolonged patient pathway, such as specific pre-treatments and/or concomitant medications, such as lymphodepletion (e.g., prior to CAR T-cell product administration) and/or immunosuppression (e.g., prior to AAV vector-based gene therapy product administration). Production times for autologous cell-based ATMPs may require patients to be treated with bridging therapies. There can be an issue of the patient's ability to wait for delayed administration of an ATMP (e.g., autologous product). There might also be a need to treat adverse events related to the mechanism of action and these can affect the efficacy of the ATMP.

Furthermore, there may be special procedures to administer the product to patients and ensure delivery to the target site in the body. The route of administration may involve invasive procedures and thus present risks more substantial than those for typical intravenous or subcutaneous injection.

**Conclusion**:

ATMPs are medicines that often treat diseases which were once considered untreatable and, in some cases, may address the underlying cause of disease. They encompass a wide range of structural modalities and complexities, and often present unique challenges that do not fit readily within the current regulatory paradigm. Developing regulatory guidance for ATMPs is challenging due to the diverse product types and manufacturing processes, modes of action, and the rapid evolution of associated technologies. In-depth integration of knowledge across the disciplines (i.e., quality, nonclinical, and clinical) is required to develop these innovative products and comprehensively assess their benefit-risk profile. Risk-based and non-traditional approaches with proper justification are often needed to support the development of cell and gene therapy products.

Based on the special considerations that make ATMPs different from traditional medicinal products, which are provided in the High Level Principles section of this document, the ICH CGTDG assessed existing ICH guidelines across all disciplines (ICH Q, S, E, and M guidelines) and those currently undergoing revision, and identified and prioritized topics that need to be addressed to support the ATMP field moving forward. The ICH CGTDG generated a strategic roadmap of prioritized recommendations for new ICH guidelines, revisions or annexes to existing ICH guidelines, or suggestions to provide illustrative examples in training materials for existing ICH guidelines. Where traditional approaches may be unsuitable for ATMPs, the ICH CGTDG worked collaboratively to identify areas where alternative approaches may need to be established in future guidelines. While the recommendations and high level principles in this paper may serve as the basis for future harmonised guidelines, neither the recommendations nor the high level principles are to be understood as scientific guidance.

## GLOSSARY

**Advanced therapy medicinal products (ATMP):**

Applying the WHO definition[8], ATMPs are "any cell or gene therapy product or tissue engineered product that has been substantially manipulated and/or performs a different function in the recipient than in the donor. ATMPs are usually produced from genetically modified and/or substantially manipulated somatic cells or tissues. ATMPs also include nucleic acids, viral and non-viral vectors, recombinant bacterial cells, and recombinant oncolytic viruses".

**Cell therapy product:**

Applying the WHO definition[8], "a product composed of human nucleated cells intended for replacement or reconstitution, and/or for the treatment or prevention of human diseases or physiological conditions, through the pharmacological, immunological or metabolic action of its cells or tissues".

**Combined ATMPs**:

Applying the WHO definition [8], "ATMPs that include a medical device(s), scaffold or matrix as an integral part of the product and where the device or additional supporting structure has a role/function in the product's overall effect and is not intended to be removed or used solely for administration purposes".

**Gene editing**:

Applying the WHO definition [8], "a method which allows for genetic material to be added, removed or altered in a sequence-specific manner in the genome. Currently, the most commonly used approaches are based on zinc finger nucleases (ZFN), transcription activator-like effector nucleases (TALEN) or clustered regularly interspersed short palindromic repeats (CRISPR) together with Cas9-endonuclease (CRISPR Cas9)".

**Gene therapy product**:

Applying the WHO definition [8], "a medicinal product containing nucleic acids (for example, plasmids, messenger RNA (mRNA) or DNA) that are intended to regulate, repair, replace, add/or delete a genetic sequence. The intended therapeutic effect is dependent upon the encoded gene used. Gene therapy products include those containing non-viral vectors (for example, lipid nanoparticles) or viral vectors that are used in vivo, as well as cells that have been modified by these types of vectors *ex vivo*. They may contain plasmids, mRNA or DNA, and may also include oncolytic viruses that are not genetically modified to express a transgene". (Within this definition, gene edited products are considered to be gene therapy products. However, vaccines intended to elicit an immune response to prevent infectious diseases (for example, mRNA, plasmid DNA or viral-vectored vaccines) are excluded from this definition and are not considered to be gene therapy products within the definition of an ATMP. It should be noted that the scope of what constitutes a gene therapy product may vary between regulatory authorities and, in some jurisdictions, might include prophylactic vaccines against infectious diseases.)".

**Tissue engineered products:**

Applying the WHO definition [8], "a medicinal product composed of nucleated human cells that are substantially manipulated and/or used in a non-homologous way, and intended for the repair, replacement, reconstitution or regeneration of tissues. Some tissue engineered products may incorporate medical devices and/or natural or artificial scaffolds such as extracellular matrix proteins".

## REFERENCES


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3. Q5A (R2) (Annex 6) Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin
4. ICH Q1 (R1) Stability testing of drug substances and drug products
5. ICH Q6 (R1) Revision of the specifications guidelines
6. ICH M4Q (R2) The common technical document (CTD) for the registration of pharmaceuticals for human use: Quality
7. ICH E23, Considerations for the Use of Real World Evidence (RWE) to Inform Regulatory Decision Making with a focus on Effectiveness of Medicines
8. World Health Organization TRS 1048 – Annex 3: Considerations in developing a regulatory framework for human cells and tissues and for advanced therapy medicinal products (2023)
9. ICH paper, "General Principles to Address Virus and Vector Shedding" (2009)
10. ICH paper, "General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors." (2006)
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12. Su, M-C, Dey, A., Maddah, E., Mugundu, G.M., and Singh, A.P. Quantitative pharmacology of dual-targeted bicistronic CAR-T-cell therapy using multiscale mechanistic modeling. CPT Pharmacometrics Syst Pharmacol (2025) 14:229–45
13. Pharmaceutical Inspection Co-operation Scheme (PIC/S) GMP Guide: Annex 2A Manufacture of advanced therapy medicinal products for human use (2022), PE 009-16 (Annexes)

**ANNEX I: CRITERIA USED FOR ASSESSING TOPICS**:

1. Regulator and sponsor experience of burden to regulatory review and approval. Issues identified by both developers and regulators as barriers to ATMP development, registration, and lifecycle management.
2. Technical maturity of issues where higher current scientific and technical understanding is prioritized. An indication of high maturity may be the existence of national/regional guidelines.
3. Current level of divergence in regulatory expectations between regions.
4. Opportunity to address issues and harmonise expectations in ICH guidance. Considered whether a new ICH guidance would be needed or revision to an existing ICH guideline. Also considered whether current and recent past procedural ICH activities addressed the issue.

**ANNEX II: DG MEMBER COUNTRY EXISTING REGULATIONS AND GUIDANCE FOR ATMPS (UPDATED DEC 2024)**:

*Annex II Explanatory Note:* The Regulations and Guidance listed in Annex II were considered interim deliverables of the ICH CGTDG that were intended to illustrate the global landscape of ATMP-relevant regulatory frameworks (e.g., regulations, guidance documents, guidelines) as of December 2024. Members and observers of the ICH CGTDG listed these documents from their respective countries/regions. This listing should not be considered comprehensive or compiled in a standardized way given regional differences in product classification and regulatory frameworks for ATMPs. Annex II is simply included as supportive information to the ICH CGTDG work and may also be a useful centralization of such information. There is no expectation for ICH to maintain or update this list in the future.

| # | Specific Country, Regulatory Authority | Title | Weblinks |
|---|---|---|---|
| 1 | ANPP, Algeria, | N/A | None/Defaults to Biologics Framework |

| | | | |
|---|---|---|---|
| 2 | ANMAT, Argentina | Disposition 179/2018: ADVANCED THERAPY MEDICINES - REQUIREMENTS, DEMANDS, AND CLASSIFICATION | Disposición 179/2018 \| Argentina.gob.ar |
| 3 | ANMAT, Argentina | Disposition 4159/2023: Guide to Good Manufacturing Practices for Manufacturers, Importers/Exporters of Medicines for Human Use | BOLETIN OFICIAL REPUBLICA ARGENTINA - ADMINISTRACIÓN NACIONAL DE MEDICAMENTOS, ALIMENTOS Y TECNOLOGÍA MÉDICA - Disposición 4159/2023 |
| 4 | ANMAT, Argentina | Official communication: International Reference Guides for Advanced Therapy Medicines | https://www.boletinoficial.gob.ar/detalleAviso/primera/223014/20191205 |
| 5 | ANVISA, Brazil | IN 270/2023 - Good Manufacturing Practices to Advanced Therapy Products (harmonized with PIC/S Annex 2A requirements), as a complement to RDC 658/2022 (GMP for Medicines). | https://anvisalegis.datalegis.net/action/ActionDatalegis.php?acao=abrirTextoAto&tipo=INM&numeroAto=00000270&seqAto=000&valorAno=2023&orgao=DC/ANVISA/MS&codTipo=&desItem=&desItemFim=&cod_menu=1696&cod_modulo=134&pesquisa=true |
| 6 | ANVISA, Brazil | RDC 658/2022 - General Guidelines for Good Manufacturing Practices for Medicines (all medicinal products) | https://anvisalegis.datalegis.net/action/ActionDatalegis.php?acao=abrirTextoAto&tipo=RDC&numeroAto=00000658&seqAto=000&valorAno=2022&orgao=RDC/DC/ANVISA/MS&codTipo=&desItem=&desItemFim=&cod_menu=1696&cod_modulo=134&pesquisa=true |
| 7 | ANVISA, Brazil | RDC 672/2022 General Guidelines for Good Manufacturing Practices of Active Pharmaceutical Ingredients | https://anvisalegis.datalegis.net/action/ActionDatalegis.php?acao=abrirTextoAto&tipo=RDC&numeroAto=00000672&seqAto=000&valorAno=2022&orgao=RDC/D |

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|---|---|---|---|
| | | | C/ANVISA/MS&codTipo=&desItem=&desItemFim=&cod_menu=1696&cod_modulo=134&pesquisa=true |
| 8 | ANVISA, Brazil | RDC 34/2014 – Good Practices in the Blood Cycle (It applies, where appropriate, to the requirements for the collection of starting material for ATMPs) | https://anvisalegis.datalegis.net/action/ActionDatalegis.php?acao=abrirTextoAto&tipo=RDC&numeroAto=00000034&seqAto=000&valorAno=2014&orgao=RDC/DC/ANVISA/MS&codTipo=&desItem=&desItemFim=&cod_menu=1696&cod_modulo=134&pesquisa=true |
| 9 | ANVISA, Brazil | RDC 505/2021 – Marketing Authorization of advanced therapy product. | https://anvisalegis.datalegis.net/action/ActionDatalegis.php?acao=abrirTextoAto&tipo=RDC&numeroAto=00000505&seqAto=000&valorAno=2021&orgao=RDC/DC/ANVISA/MS&codTipo=&desItem=&desItemFim=&cod_menu=1696&cod_modulo=134&pesquisa=true |
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| 252 | FDA, United States | Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up; Guidance for Industry | See Title column |
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| 261 | FDA, United States | Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products \| FDA | See Title column |
| 262 | FDA, United States | Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products; Guidance for Industry | See Title column |
| 263 | FDA, United States | Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products; Draft Guidance for Industry | See Title column |
| 264 | FDA, United States | Considerations for the Use of Human-and Animal-Derived Materials in the Manufacture of Cell and Gene Therapy and Tissue-Engineered Medical Products | See Title column |
| 265 | FDA, United States | Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products \| FDA | See Title column |
| 266 | FDA, United States | Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence \| FDA | See Title column |

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| 267 | FDA, United States | Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products; Guidance for Industry | See Title column |
| 268 | FDA, United States | Evaluation of Devices Used with Regenerative Medicine Advanced Therapies; Guidance for Industry | See Title column |
| 269 | FDA, United States | Expedited Programs for Regenerative Medicine Therapies for Serious Conditions; Guidance for Industry | See Title column |
| 270 | FDA, United States | Frequently Asked Questions — Developing Potential Cellular and Gene Therapy Products | See Title column |
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| 272 | FDA, United States | Guidance for Industry: BLA for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic and Immunologic Reconstitution in Patients with Disorders Affecting the Hematopoietic System | See Title column |
| 273 | FDA, United States | Guidance for Industry: Cellular Therapy for Cardiac Disease | See Title column |
| 274 | FDA, United States | Guidance for Industry: Clinical Considerations for Therapeutic Cancer Vaccines | See Title column |

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| 275 | FDA, United States | Guidance for Industry: Considerations for Allogeneic Pancreatic Islet Cell Products | See Title column |
| 276 | FDA, United States | Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy | See Title column |
| 277 | FDA, United States | Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products | See Title column |
| 278 | FDA, United States | Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products | See Title column |
| 279 | FDA, United States | Guidance for Industry: Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage | See Title column |
| 280 | FDA, United States | Human Gene Therapy for Hemophilia; Guidance for Industry | See Title column |
| 281 | FDA, United States | Human Gene Therapy for Neurodegenerative Diseases; Guidance for Industry | See Title column |
| 282 | FDA, United States | Human Gene Therapy for Rare Diseases; Guidance for Industry | See Title column |
| 283 | FDA, United States | Human Gene Therapy for Retinal Disorders; Guidance for Industry | See Title column |
| 284 | FDA, United States | Human Gene Therapy Products Incorporating Human Genome Editing; Draft Guidance for Industry | See Title column |
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| | | Immunologic Reconstitution in Patients with Disorders Affecting the Hematopoietic System - Guidance for Industry and FDA Staff | |
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| 287 | FDA, United States | Long Term Follow-up After Administration of Human Gene Therapy Products; Guidance for Industry | See Title column |
| 288 | FDA, United States | Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products; Draft Guidance for Industry | See Title column |
| 289 | FDA, United States | Manufacturing Considerations for Licensed and Investigational Cellular and Gene Therapy Products During COVID-19 Public Health Emergency; Guidance for Industry | See Title column |
| 290 | FDA, United States | Master Protocols for Drug and Biological Product Development \| FDA | See Title column |
| 291 | FDA, United States | Potency Assurance for Cellular and Gene Therapy Products; Draft Guidance for Industry | See Title column |
| 292 | FDA, United States | Rare Diseases: Considerations for the Development of Drugs and Biological Products \| FDA | See Title column |
| 293 | FDA, United States | Recommendations for Microbial Vectors Used for Gene Therapy; Guidance for Industry | See Title column |

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| 294 | FDA, United States | Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use; Guidance for Industry and Food and Drug Administration Staff | See Title column |
| 295 | FDA, United States | Safety Testing of Human Allogeneic Cells Expanded for Use in Cell-Based Medical Products | See Title column |
| 296 | FDA, United States | Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception; Guidance for Industry | See Title column |
| 297 | FDA, United States | Studying Multiple Versions of a Cellular or Gene Therapy Product in an Early-Phase Clinical Trial; Guidance for Industry | See Title column |
| 298 | FDA, United States | Voluntary Consensus Standards Recognition Program for Regenerative Medicine Therapies \| FDA | See Title column |
| 299 | FDA, United States | Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) - Small Entity Compliance Guide; Guidance for Industry | See Title column |
| 300 | FDA, United States | Use of Nucleic Acid Tests to Reduce the Risk of Transmission of West Nile Virus from Living Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) \| FDA | See Title column |
| 301 | FDA, United States | Revised Recommendations for Determining Eligibility of Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products Who Have | See Title column |

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