

POINTS TO CONSIDER TO PROMOTE CONVERGENCE AND RELIANCE APPROACHES FOR ATMP

EXECUTIVE SUMMARY

Cell, Tissue, and Gene therapies offer significant potential to treat diseases with high unmet medical needs, and consist of Human Cell and Tissue products for medical use (HCTs) and Advanced Therapy Medicinal Products (ATMPs).

One of the challenges in regulating Cell, Tissue, and Gene therapies is to establish a clear definition that determines product classification for ATMPs and therefore the applicability of the corresponding regulations. Considering the lower regulatory requirements applied to HCTs, it is of most importance that these definitions are clear and the corresponding classifications are transparent to regulatory authorities and sponsors.

This paper discusses the need to converge on the definitions and classification of ATMPs in order to foster reliance and/or recognition approaches to enable patients' access to ATMPs. The list of recommendations is summarized opposite:

Promote harmonization and recognition of product classification

RECOMMENDATIONS 1-2

Facilitate reliance, recognition and collaboration across ATMP lifecycle

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Encourage harmonization of accreditation and standardization programs

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Waive in-country testing

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Use of "universal label" and electronic options

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Recognize GMP compliant certification

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Harmonize and streamline ATMP-GMO risk assessment

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LEGAL FRAMEWORK AND CLASSIFICATION OF ATMPs

The ATMP field is evolving rapidly and legal and regulatory frameworks have been developed for “traditional” medicinal products, which do not account for the unique nature of these therapeutics, and can prevent access of these therapies to patients in general and/or in a timely manner.

Lack of Established Legal/Regulatory Frameworks for ATMPs in Many Countries

Many countries globally do not have the expertise and/or resources to develop a regulatory framework to support timely and efficient introduction of ATMPs.

Some countries are using existing medicinal product regulation to manage ATMPs. These existing regulatory frameworks often do not appropriately fit the needs of ATMPs due to their unique characteristics and complexity, resulting in delayed access to these innovative treatments.

Several countries have established specific legal and regulatory frameworks to regulate ATMPs. For example, the European Medicines Agency (EMA), US Food and Drug Administration (US FDA) and Japan Ministry of Health, Labour and Welfare (MHLW) have specific laws and extensive lists of procedural or technical guidelines. While many countries are currently developing their own ATMP regulatory frameworks, the risk of developing divergent guidelines across regions poses significant challenges to sponsors with multinational development programs and plan for global registration.¹

While ATMPs could be regulated in different manners, e.g., within the existing framework of biological products or through creation of ATMP-specific regulation, most countries will benefit from staying aligned with more established systems that have already been put into practice, such as US FDA or EMA. Legal/regulatory frameworks should be sufficiently flexible to account for current and future modalities, encompass the entire product lifecycle (e.g., clinical trials, approval and post-approval changes) and enable use of recognition and reliance processes to enhance collaboration between NRAs.

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Need for Clear Definitions and Transparent Classification

The overarching product category of Cell, Tissue, and Gene therapies encompasses “Human Cell and Tissue products for medical use (HCTs)” and ATMPs. One of the first challenges in regulating ATMPs is to develop clear definitions that determine product classification, and thus the corresponding regulation that applies to these products.

ATMPs consist of different categories of Medicinal Products (MP): Cell Therapy MP, Gene Therapy MP, Tissue engineered MP or combinations thereof with or without devices. As for any medicinal product, sponsors must prospectively demonstrate to the regulatory authority that ATMPs present acceptable quality, safety, and efficacy profiles, before they can be placed on the market. ATMPs are manufactured according to validated processes, are subject to release procedures (including compliance to registered specifications) and follow specific post-authorization pharmacovigilance and change control requirements.

ATMPs are differentiated from “human cells, tissues, and cellular and tissue-based products for medical use” (HCTs or HCT/Ps) which are minimally manipulated cells and tissues used in the same essential function in the recipient as in the donor (i.e., “homologous use”). HCTs are generally considered as established medical procedures performed in hospitals and follow different requirements and authorization processes (e.g., not requiring prospective demonstration of efficacy through clinical trials and different quality standards are applied).

As HCTs present a lower risk to patients, they are often covered by other legal frameworks such as transplant regulations, aimed largely at the prevention of contamination and disease transmission. HCTs are generally not considered as “medicinal products”, and are not subject to medicinal product / pharmaceutical registration requirements.

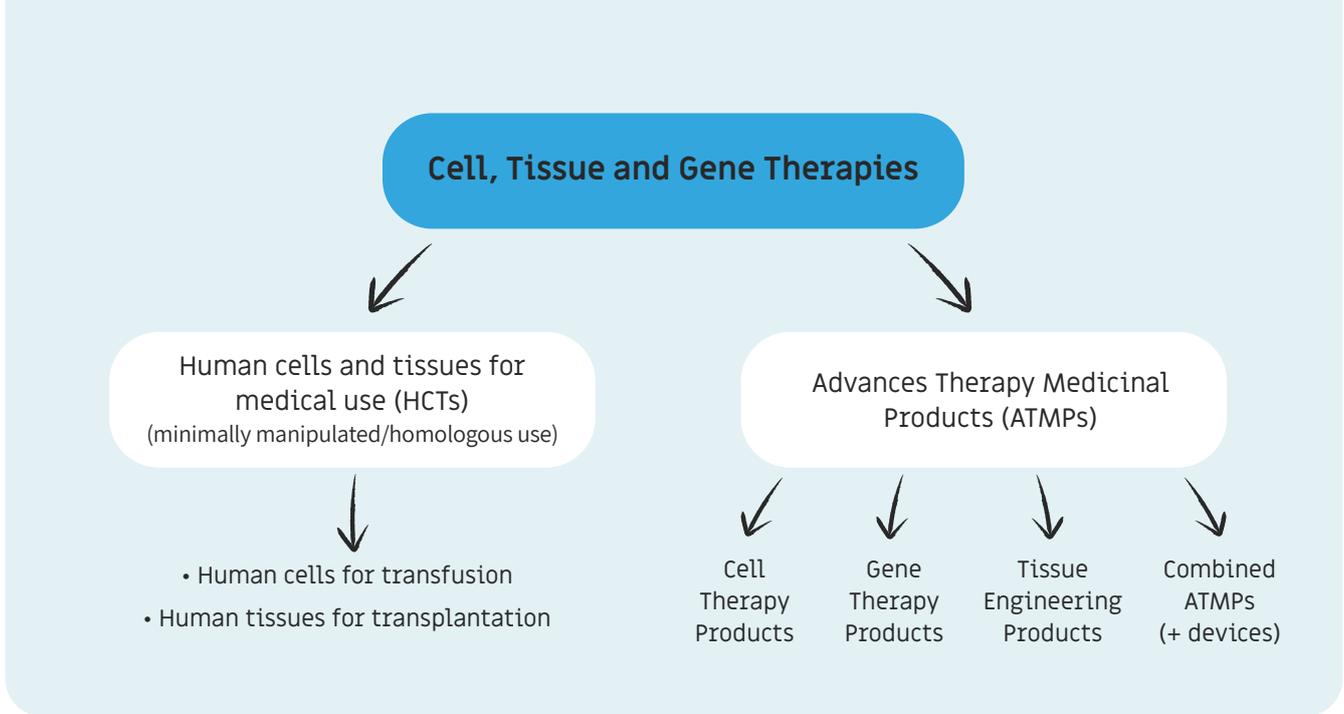


Figure 1. Classification adapted from “WHO considerations on regulatory Convergence of Cell and Gene Therapy Products”, WHO/CGTPs/Draft/16 December 2021.²

The terms “Cell Therapy Products (CTPs)” can describe cells that are minimally manipulated for homologous use (i.e., considered as HCTs) or cells that undergo substantial manipulation and are used in different essential functions as the donor (i.e., considered as ATMP).

An example where definitions can lead to different classification is related to administration of genetically modified cells to patients. Depending on whether the intended effect is directly related to the transgene or not, such a product could be considered as Cell Therapy Medicinal Product or ex vivo Gene Therapy Medicinal Product.

Considering the lower regulatory requirements applied to HCTs (as compared to ATMPs), it is of utmost importance that the delineation between HCTs and ATMPs is clear and harmonized. Furthermore, transparent publication of classification decisions (e.g., Classification recommendation published by EMA CAT³), particularly for borderline products, is fundamental to drive consistent classification to anticipate how a given product will be regulated in a specific country.

RECOMMENDATIONS

1. Establish clear definitions (i.e., in accordance to definitions established by WHO with corresponding legal/regulatory frameworks) for HCTs and ATMPs.
2. Promote recognition of classification published by reference National Regulatory Authorities (NRA) and identify national authority/institution that will be responsible for product classification and transparent communication of the decisions.

REGULATORY RECOGNITION AND RELIANCE ACROSS THE PRODUCT LIFECYCLE

As recommended by WHO Good Reliance Practices⁴, adoption of reliance approaches can improve patient access to medical products. Regulatory reliance is increasingly being used by National Regulatory Authorities (NRAs) of different maturity levels. This concept is actively promoted by organizations such as WHO, the Pan American Health Organization (PAHO) and the EMA as a mechanism for NRAs to better manage resources, whilst simultaneously strengthening regulatory systems. Reliance benefits patients, health care providers, industry, national governments, and international development partners by facilitating and accelerating access to quality-assured, effective, and safe medical products.

The World Health Organisation (WHO) defines:

- **Reliance:** act whereby a regulatory authority in one jurisdiction may take into account/give significant weight to work performed by another regulator or other trusted institution in reaching its own decision.
- **Recognition:** the routine acceptance of the regulatory decision of another regulator or other trusted institution. Recognition indicates that evidence of conformity with the regulatory requirements of country A is sufficient to meet the regulatory requirements of country B.

As with other medicinal products, ATMPs can benefit from recognition and reliance approaches. Such approaches are particularly valuable for novel and complex products, and those for treatment of rare/ultra-rare disease, and for countries with limited legal/regulatory framework or limited experience in managing these ATMPs. Various forms of reliance could be applied depending on the NRA specificities, utilizing recognition of assessments or decisions from a reference NRA.

Regulatory reliance can improve patient access to ATMPs by facilitating product registration, as well as with inspection (e.g., Mutual Recognition Agreement of GMPs), lot release or in-country testing.

Approval by experienced regulatory agencies, such as the US FDA or EMA, can also form the basis for approval in other countries across the lifecycle of the product (e.g., clinical trials, marketing authorization, post approval changes).

Access to some products can be delayed in some countries, due to difference in data requirements disqualifying the use of reliance or recognition pathways. For example, risk based assessment may be used by US FDA or EMA to approve products for unmet medical need with reduced data package (e.g., based on phase 2 clinical trial), yet will not fulfil local national requirements (e.g., requirement of phase 3 clinical trial), and thus may not qualify for a reliance or recognition pathway. It is recommended that NRAs adopt similar risk-based approach to data requirements as the reference country when implementing reliance or waive specific country requirements in order to enable reliance pathways.

NRAs could also partner with other NRAs or leverage regulatory work of other trusted authorities. There may be opportunities to expand the scope of existing health authority collaborations to include ATMPs.

RECOMMENDATIONS

3. Enable recognition and reliance approaches across the lifecycle of ATMPs. This should include products approved through expedited regulatory pathways.
4. NRAs are recommended to adopt a similar risk-based approach to data requirements consistent with the reference country filing package when implementing reliance.
5. Expand the scope of existing collaboration mechanisms for review of applications among several health authorities (e.g., marketing authorization, clinical trial, post marketing, scientific advice) to explicitly include ATMPs.
6. Promote participation in pilot programs for joint review and work-sharing (e.g., clinical trial, scientific advice) which allow expedited review pathways.

EXAMPLES OF ACCESS-LIMITING REQUIREMENTS

SUPPLY, QUALIFICATION OF COLLECTION CENTERS AND IN-COUNTRY TESTING

ATMPs are generally supplied directly on request “made to order” or “off the shelf” from the manufacturing site to treatment centers, under full oversight of the manufacturer. This may allow customization of individual pack generation to given treatment center (e.g., weight-based dosing requirements, individualized therapies). Batches are often not manufactured or stored in the country where the patient is being treated. ATMPs are typically stored at ultra-low temperature ($\leq -60^{\circ}\text{C}$) and transported via ultra-cold chain shipment.

For ATMPs (including therapies using starting material from human origin), Chain-of-Custody (CoC) and Chain-of-Identity (CoI) unambiguously ensure the bidirectional tracking of products and allow end-to-end product traceability from the collection (e.g., blood, tissue, cells, biopsy) to product administration.

Due to the lack of harmonization in regulatory requirements, manufacturers are applying their own standards, leading to different approaches regarding certification, onboarding, audit and management of collection sites. This non-harmonized approach leads to redundancies and an unnecessary administrative burden for biospecimen collection sites, pathology labs, or treatment centers. Such burden could be reduced by converging existing regulation and recognition of existing fit-for-purpose regulations and accreditations, specific to the field of cell, blood and tissue collection/handling (e.g., FACT⁵, JACIE⁶).

In-country testing of ATMPs⁷ is extremely challenging and time consuming (as they are directly supplied to treatment centers, the testing often uses non-traditional analytical technology which may not be available in all countries), and many assays used to control ATMPs are complex and challenging to implement. ATMP batch sizes are usually small because they are typically for the treatment of a small number of patients or a single patient (e.g., individualized therapy). In-country testing would consume a large

fraction of a batch relative to that required for patient treatment. Furthermore, testing in accordance with local pharmacopeial monographs (e.g., sample requirements microbial testing), if possible (e.g., within product shelf life), can also consume a large fraction of a batch, and can significantly reduce the amount of material available for patient treatment (including clinical trials).

Given the specific supply chain process, country-specific requirements such as sampling/ in-country testing / retention sample/government wholesale, and customs obligations can lead to cold chain interruption, and could jeopardize product integrity, collection or distribution, and thus delay or prevent patient access to ATMPs.

RECOMMENDATIONS

7. Promote convergence of existing regulation (requirements and interpretation) and recognition of existing fit-for-purpose regulations and accreditations specific to the field of cell, blood and tissue collection/handling (e.g., FACT, JACIE).
8. Encourage global coordination on accreditations and standardization by an international institution (such as the WHO and Standards Coordinating Body).
9. Waive in-country testing and rely on Certificates of Analysis (CoA) for products manufactured in facilities certified by reference National Regulatory Authorities (NRA).

UNIVERSAL LABELS

The acceptance of universal labelling of the primary packaging facilitates the supply and allows the required flexibility to ship on demand. Such a universal label could include a common set of the minimum requirements for primary labelling in English, and ‘country-specific’ information in secondary packaging.

Country-specific labels are typically required for medicinal products. However, this requirement is very challenging for ATMPs. ATMPs are typically stored at ultra-low temperatures, and a primary label is often applied to the vial or cryobag prior to freezing.

Commercial labels could be applied to the primary container as part of the manufacturing process; however, the following challenges should be considered:

- The label could be applied prior to freezing; however, country-specific labelling limits the flexibility for allocating products on demand and may result in discarding high-cost products that have the wrong country-specific labels.
- The label could be applied on vial or cryobag after thawing and drying; however, this introduces an unnecessary freeze-thaw cycle which could have an impact on stability and the shelf life of the product.
- The label could be applied to the frozen vial or cryobag, but the logistics are complex and labels may lose adhesiveness over time.

Thus, there is no satisfactory method currently for labelling the primary container.

At time of labelling, demand forecast accuracy of any particular country is very low because the ATMPs are usually used for treatment of a very small patient population compared with traditional products. Moreover, the product is handled and administered in specialized facilities by highly qualified healthcare professionals usually proficient in the English language, who will have access to the secondary packaging label and the package insert in the local language.

Therefore, authorizing the use of a universal label in English on the primary packaging associated with secondary packaging and product information in the local language

(ideally in electronic format) would significantly facilitate supply for on-demand ATMPs. The use of reliance pathways in the context of labelling is also of utmost importance, and it would also ensure that the content is aligned with the reference market across the product lifecycle.

Additionally, mobile scanning technology (e.g., 2-D matrix code) features could be included in the primary label, supporting easy access to relevant information by the health care professionals. This mobile technology feature would provide the required labelling information for health care professionals and many countries, and in the local language. The use of mobile scanning technology has also been implemented in EU⁸ and US.

An example of labelling exemptions for orphan medicinal products can be found in EU legislation⁹, where the product is not intended to be delivered directly to the patient, or where there are severe problems with respect to the availability of the product and similar guidelines could be introduced globally to allow implementation of a universal label.

In addition, ATMPs are administered by experienced specialists that will have access to the secondary packaging label and the package insert in the local language, thus, the risks due to usage of universal English labelled primary packaging are relatively negligible.

RECOMMENDATIONS

10. Allow the use of a standardized universal label, in English language, on primary packaging at which temperature the product should be stored, with labels and inserts that conform to regional requirements for labelling details and language, but are aligned to reference market content.

11. Promote the use of mobile technology features in the primary label (e.g. 2-D matrix codes) to support access of relevant information.

GMP STANDARDS AND INSPECTION

The Pharmaceutical Inspection Co-operation Scheme (PIC/S)¹⁰ has developed ATMP-specific GMP guidelines that acknowledges ATMP specifics and introduces flexibilities for manufacturing.

NRAs are encouraged to adopt PIC/S Annex 2A ‘Manufacture of advanced therapy medicinal products for human use’, which will allow for standardization of GMP requirements across the globe. It addresses ATMP specificities (e.g., start of GMP process) and introduces flexibilities (e.g., regarding reference sample quantities, process validation strategies). Broad adoption of PIC/S Annex 2A would promote capacity building, provide training opportunities, and more detailed understanding on new concepts required for ATMP manufacturing.

Furthermore, it would also support GMP compliance inspections, opening an opportunity for reliance upon a reference NRA. This would accelerate the compliance inspection process and reduce redundancy.

RECOMMENDATIONS

12. Adopt PIC/S Annex 2A ‘Manufacture of advanced therapy medicinal products for human use’, which supports recognition of GMP compliance certifications by reference NRAs and thus inclusion of ATMPs in mutual recognition agreements.

GENETICALLY MODIFIED ORGANISM (GMO) REQUIREMENTS

The differences in expectations and processes for GMO risk assessments (of ATMPs that consist of, or contain, GMOs (GMO-ATMP)) result in a high regulatory burden and potential delay to the initiation of clinical trials. In many countries, regulations (requirements and processes) primarily established for agricultural applications (plants and crops) are also applied to ATMPs.

While a GMO risk assessment may be part of an application for marketing authorization in the region, it should not be a default requirement for clinical trials. A GMO-ATMP, which has been assessed in multiple clinical trials, will allow the sponsor to provide a more thorough assessment of safety, biodistribution and shedding on a larger number of subjects, rather than that based on non-clinical animal studies, as would be provided for first in human clinical trials. Furthermore, the removal of the requirement of a GMO-ATMP risk assessment for a Clinical Trial Application (CTA) removes potential delays to the commencement of clinical trials.¹¹

In many regions, the GMO regulatory framework that was established for agricultural applications is inappropriately applied to ATMPs. GMO risk assessment requirements that are appropriate for wide-scale deliberate release of GMO plants that may be able to propagate, do not appropriately reflect the negligible risks when ATMPs are studied in clinical trials in a controlled environment.

A GMO risk assessment should not be required in clinical trials if the GMO-ATMP is unable to survive and replicate outside of the intended clinical trial recipient.

Regardless of whether the gene delivery vector is designed to be replication-incompetent, replication-competent, or selectively replication-competent (for example, in p53-deficient tumour cells) all viral vector particles have no ability to spread in the environment.

After direct administration, replication-incompetent viral vector particles (such as those based on the commonly used recombinant adeno-associated virus) that have not been taken up by cells of the body exist at only very low levels in human (i.e., upon dilution within the body) and, if excreted, are not anticipated to be infectious.

Furthermore, if released into the environment, nucleic acids released from viral vectors or human genetically modified cells would be rapidly degraded.

Waiving the requirement for submission of a GMO-ATMP risk assessment at the clinical stage is appropriate and can help secure patient access to ATMPs.

RECOMMENDATIONS

13. At the stage of a clinical trial application (CTA), a GMO risk assessment should not be required if the GMO-ATMP is not able to survive and replicate outside of the intended clinical trial recipient, or if the transgene sequence is not harmful.

14. Where GMO risk assessment exemptions do not apply, promote the use of a “universal” or at least, harmonised principles.

15. If required for registration, and if policy frameworks allow, an approved GMO risk assessment performed in reference countries/regions should be recognized.

- 1 IPRP’s summary of diverse regulatory frameworks, IPRP CTWG-GTWG Frameworks 2021_0811_1.pdf July 2021
- 2 https://cdn.who.int/media/docs/default-source/biologicals/ecbs/who-public-consultation_cgtp-white-paper_16_dec_2021.pdf?sfvrsn=18f6c549_5
- 3 https://www.ema.europa.eu/documents/other/scientific-recommendations-classification-advanced-therapy-medicinal-products_en.xlsx
- 4 World Health Organization. Good reliance practices in the regulation of medical products: high level principles and considerations. Jun 29 2021: <https://www.who.int/publications/i/item/55th-report-of-the-who-expert-committee-on-specifications-for-pharmaceutical-preparations>
- 5 <https://www.factglobal.org>
- 6 <https://www.ebmt.org/jacie-accreditation>
- 7 IFPMA position: In-country Testing of Advanced Therapy Medicinal Products. February 2022 (www.ifpma.org/resource-centre/position-paper-in-country-testing-of-advanced-therapy-medicinal-products)
- 8 EMA/493897/2015 Rev. 1: Mobile scanning and other technologies in the labelling and package leaflet of centrally authorised medicinal products (https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/mobile-scanning-other-technologies-labelling-package-leaflet-centrally-authorized-medicinal-products_en.pdf) - [European medicines regulatory network adopts EU common standard for electronic product information](https://www.ema.europa.eu/en/news/european-medicines-regulatory-network-adopts-eu-common-standard-for-electronic-product-information) | [European Medicines Agency \(europa.eu\)](https://www.ema.europa.eu/)
- 9 Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (EUR-Lex - 02001L0083-20190726 - EN - EUR-Lex (europa.eu))
- 10 PIC/s is a non-binding, informal cooperative arrangement between Regulatory Authorities in GMP with currently 54 global participating authorities (Europe, Africa, America, Asia and Australia). <https://picscheme.org/en/about-international-co-operation>.
- 11 Call for More Effective Regulation of Clinical Trials with Advanced Therapy Medicinal Products Consisting of or Containing Genetically Modified Organisms in the European Union - <https://pubmed.ncbi.nlm.nih.gov/33843251>