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# WHO approach towards the development of a global regulatory framework for cell and gene therapy products

NOTE:

This document has been prepared for the purpose of inviting comments and suggestions on the proposals contained therein, which will then be considered by the Expert Committee on Biological Standardization (ECBS). Publication of this early draft is to provide information about the proposed document- *WHO approach towards the development of a global regulatory framework for cell and gene therapy products*, to a broad audience and to ensure the transparency of the consultation process.

**The text in its present form does not necessarily represent the agreed formulation of the ECBS. Written comments proposing modifications to this text MUST be received by 9 September 2022 using the Comment Form available separately** and should be addressed to the Department of Health Products Policy and Standards, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland. Comments may also be submitted electronically to the Responsible Officer: **Dr Richard Isbrucker at email: isbruckerr@who.int**.

The outcome of the deliberations of the Expert Committee will be published in the WHO Technical Report Series. The final agreed formulation of the document will be edited to be in conformity with the "WHO style guide, second edition" (KMS/WHP/13.1).

This document is intended to describe WHO's current thinking on the regulation of Cell and Gene Therapy Products, to promote convergence, and encourage the Member States to strengthen their regulatory system on both human cells and tissues (HCTs) and advanced therapy medicinal products (ATMPs). This document is not intended to be a comprehensive overview of regulatory requirements for either HCTs or ATMPs or the different regulatory frameworks that currently exist in different jurisdictions. The objective of this document is to outline some of the fundamental principles that are important for providing adequate regulatory oversight for different types of cell and gene therapy products and it should be reviewed in that context. In the future, WHO will provide a more comprehensive overview and guidance on specific topics relevant to regulation of HCTs and ATMPs.

# WHO approach towards the development of a global regulatory framework for cell and gene therapy products

## Abbreviations

| | |
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| ASEAN | Association of Southeast Asian Nations |
| ATMP | Advanced Therapy Medicinal Product |
| AVAREF | African Vaccine Regulatory Forum |
| CD | Cluster of differentiation |
| CRP | Collaborative Review Procedure |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| GMP | Good Manufacturing Practice |
| HCT | Human cells and tissues for medical use |
| HIV | Human immunodeficiency virus |
| ICDRA | International Conference of Drug Regulatory Authorities |
| LMICs | Low- and Middle-Income Countries |
| NRA | National Regulatory Authority |
| PIC/S | Pharmaceutical Inspection Co-operation Scheme |
| WHO | World Health Organization |

This document is intended to describe WHO's current thinking on the regulation of Cell and Gene Therapy Products, to promote convergence, and encourage the Member States to strengthen their regulatory system on both human cells and tissues (HCTs) and advanced therapy medicinal products (ATMPs). This document is not intended to be a comprehensive overview of regulatory requirements for either HCTs or ATMPs or the different regulatory frameworks that currently exist in different jurisdictions. The objective of this document is to outline some of the fundamental principles that are important for providing adequate regulatory oversight for different types of cell and gene therapy products and it should be reviewed in that context. In the future, WHO will provide a more comprehensive overview and guidance on specific topics relevant to regulation of HCTs and ATMPs.

## Introduction

The use of cells, tissues, and gene therapy products for the treatment of human diseases or physical conditions has developed wide interest due to their potential to address serious unmet medical needs. These cell-, tissue- and gene-based therapies and products (1) encompass a remarkably broad range of complexity, ranging from the relatively simple (such as unprocessed autologous cells and tissue grafts) to the highly complex (such as genetically modified cells). Many countries have established an effective legal framework and regulations reflective of the diversity and complexity of this class of therapies and products in order to ensure the protection of the donors and safety of the recipients.

Cells and tissues which have undergone minimal manipulation are often, but not necessarily, used to provide the same essential functions in the recipient as they do in the donor. These are defined here as human cells and tissues for medical use (HCTs). Examples of HCTs include hematopoietic stem cells for the treatment of hematological malignancies, corneas to restore sight, and skin grafts to treat burn victims. They may be derived from living donors (such as hematopoietic stem cells) or from the deceased (such as heart valves, cornea, and skin grafts), and the number and type of novel HCTs is increasing steadily with advances in medicine. HCTs typically are regulated under transfusion or transplantation rules, for which the main focus is to ensure the quality and safety of the donated material (2,3). In addition, donor protection, traceability and ethical issues of cell, tissue, and organ donation are central parts of HCT regulations (4).

Advanced therapy medicinal products (ATMPs) for human use are defined as cell and gene therapy products and tissue engineered products, which are produced not only from manipulated cells or tissues. ATMPs also include nucleic acids or suitable vectors like plasmids or viruses for either direct administration to a recipient or to isolated cells or tissues (3,5). ATMP product types are highly diverse and can include expanded autologous (patient) cells, engineered organs, viral products, genetically modified cells and novel gene editing/edited products (6,7) (see Table 1). ATMPs can also be combined with medical devices, such as scaffolds or matrices, as an integral part of the product (combined ATMPs). This variety of product types gives ATMPs the potential to address a wide range of unmet medical needs and may present inherent advantages over some existing treatments and current standards of care. These products are emerging rapidly as potentially curative treatments that could transform the management of diseases such as thalassemia, sickle cell disease, hemophilia, spinal muscular atrophy, Leber´s congenital amaurosis and many other monogenic diseases (8).

ATMPs have unique issues in their development processes that distinguish them from other pharmaceutical or biotherapeutic products. As a result, ATMPs can differ from other medicinal products in their requirements for manufacture and quality control, nonclinical assessment, clinical development, and post-market monitoring (9). An understanding of these issues is crucial for the development and establishment of a tenable regulatory framework for the oversight of these products.

ATMP manufacturing issues can stem from the origin and sourcing of the starting materials, which are commonly HCTs, and the manipulation processes the starting material undergoes to generate the therapeutic product. For cells and tissues, as well as for nucleic acids and viral vectors, these methods can be complex and require specialized facilities and techniques for product manufacturing and formulation (10). That is the case particularly for genetically modified cells and directly administered gene therapy products. Therefore, manufacturing facilities for ATMPs are usually separate from that where the starting materials are obtained and processed and as such will require their own licensing for operation. In addition, any medical device used as part of a combined ATMP or in the administration of an ATMP also requires compliance with manufacturing and marketing regulations.

The nonclinical testing of ATMPs can be challenging for many new indications and especially for orphan diseases. These challenges include finding appropriate *in vitro* systems or animal models (11) and limitations resulting from inherent differences in the immune systems of animal species and humans. For cell-based therapies where multiple receptor-ligand interactions occur between the administered cell product and the surrounding host tissue, the physiological outcome of these interactions can differ between species. Thus, whether evaluating an allogeneic or xenogeneic product within an *in vivo* model, there are likely to be differences in responses between the animal and the human. Similarly, viral vectors pose their own difficulties when studied in animal models as they can differ in their tropism and will not necessarily infect all species. Cell-based immunotherapies with or without concurrent genetic modification pose, perhaps, the greatest challenge in their nonclinical assessments due to the exquisite specificity of the immune system, and in-built mechanisms of host defense. Furthermore, for therapeutic products which utilize genome editing technology, their nonclinical testing requires the use of human cells to evaluate potential off-target effects.

Clinical development of HCTs and ATMPs require special regulatory considerations. This may include accounting for the lack of adequately documented natural history data for rare diseases as well as the need to evaluate clinical safety and efficacy in very small patient populations. Furthermore, interpretation of efficacy from controlled clinical trials for some ATMPs may be difficult if there is no suitable comparator or if the improvement in the recipients is minimal in

response to the treatment. Some ATMP products, such as systemically-administered integrating gene therapy products, may have effects that last for years or decades. Under these circumstances, it is important to ensure adequate long-term patient follow up, which itself imposes its own difficulties in product development (12).

Regardless of their regulatory expertise and maturity level, countries in all regions of the world are receiving – or have received – regulatory submissions from companies or non-profit organizations interested in providing access to these potentially transformative products which can have significant public health impact. It is important for authorities to be aware of the regulatory considerations, challenges and needs for adequate data support for these products and address them to assure the safety and efficacy of the treatments and avoid unnecessary delays in patient access.

Due, in part, to the varied nature of HCTs and ATMPs, it is not surprising that national or regional regulatory frameworks for oversight of these products have evolved somewhat differently around the world. However, despite any differences, all are intended to confer at least minimum standards to protect the donors and ensure the safety and effectiveness of the administered products. The regulatory frameworks are based on sound scientific and ethical principles and include the requirement for a comprehensive evaluation of risks vs benefits that are applicable to the different categories of HCTs and ATMPs.

Effective regulatory decision making will depend on establishing strong, risk-based regulatory frameworks for the oversight of cell and gene therapy products. The key elements of an effective regulatory framework include:

- a clear definition of the categories that constitute HCTs and ATMPs,
- a risk stratification of the HCTs and ATMPs and,
- aligning the level of regulatory control based to the different risk categories.

In most regulatory jurisdictions with existing legislations and regulations applicable to ATMPs, they are regulated as medical products to ensure quality, safety and efficacy before authorization for use in the patient population. The regulatory requirements for ATMPs differ based on the stage of development with stringency increasing as more knowledge is gathered about the product and its safety and efficacy, and the product moves from investigational to commercial use. For HCTs, the regulations concentrate on the control of possible transmission of communicable diseases and contaminants as well as the quality and safety for their intended use (2,13), whereas the regulatory expectations for ATMPs also include requirements to address the additional risks inherent in complex, highly manipulated products (14-21). Additionally, it is important to ensure that appropriate long-term post-market surveillance systems are in place,

particularly where the effects of ATMPs are expected to last for many years. In all cases, regulatory decisions for HCTs and ATMPs are based on the totality of the available information and a comprehensive benefit/risk assessment during the development phase as well as post-authorization.

Development of a regulatory framework for oversight of HCTs and ATMPs should take into consideration the regulatory authority's maturity level, staff experience and expertise in evaluating products in the different risk categories, and available resources for initial assessment and life-cycle oversight. National regulatory authorities (NRAs) with limited experience in reviewing applications for HCTs and ATMPs, or with limited resources are encouraged to have, as an integral part of their regulatory framework, mechanisms to practice evidence-based reliance on the assessments and decisions of trusted partners and NRAs with more longstanding experience and expertise in the review of these products. Utilization of regulatory reliance will help ensure increased global access to safe and effective cell and gene therapy products. As NRAs gain experience and expertise, they can review more complex applications in alignment with their increased capacity and resources.

## Purpose

The goal of WHO is to promote regulatory convergence for HCTs and ATMPs to facilitate development and access to these treatments and products, including through the practice of reliance, for patients in all regions of the world. In addition, the aim is to increase the safety of patients treated with HCTs or ATMPs by preventing exploitation from occurring in those jurisdictions without, or with inadequate regulations in place for providing oversight of the safety and efficacy of such novel products (22,23).

At the 2018 International Conference of Drug Regulatory Authorities (ICDRA) meeting (24), Member States noted the potential impact of HCTs and ATMPs for global public health and the need, especially in LMICs, to build scientific knowledge and strengthen their regulatory capacity to provide oversight of these novel products. The following areas were identified as priorities:

- Defining what HCTs and ATMPs are (what is in scope and what is out of scope)
- Developing regulatory requirements for HCTs and ATMPs which are based on sound scientific and risk-based principles
- Convergence on establishing minimum global standards for ATMPs

The ICDRA recommendation was for "WHO to develop with Member States a 'current state of the art' document capturing areas where agreement among experienced regulatory authorities

exists, noting where harmonization has yet to be achieved, and documenting existing areas of uncertainty. Areas covered could include definitions, quality attributes, standards, and clinical development pathways." (24)

The priorities that Member States identified are to:

1. Clearly describe what the categories of HCTs and ATMPs are and provide definitions of key terminology relevant in this area;
2. Summarize the existing state of ATMPs that are approved or under development, including examples of challenges in the development and where solutions have been identified;
3. Describe some key elements of a regulatory framework that support the quality, safety and effectiveness of HCTs and ATMPs including:
    a. regulatory requirements for different risk categories of products,
    b. the need for adequate oversight of products through their entire lifecycle from the investigational phase through to post-market surveillance;
4. Develop a proposal for how the regulatory framework for the risk categories could be implemented in countries with different levels of regulatory maturity, and;
5. Provide an annotated bibliography to highlight key references relevant to the manufacture, product development, and regulation of ATMPs.

The WHO Expert Committee on Biological Standardization (ECBS) also recognized that HCTs and ATMPs have great potential in the treatment of various diseases and would become important future public health interventions (25). The Committee had a clear consensus that global convergence for HCTs and ATMPs is needed and that WHO should continue collaboration with other international groups active in this area (26-28).

This document is a first step in responding to the ICDRA and ECBS recommendations and outlines the priorities and next steps, as identified by regulators from both developed and developing countries, for advancing global convergence on the regulation of HCTs and ATMPs. It also emphasizes the importance of Member States strengthening their regulatory systems for oversight of these products. Some of the issues identified as priorities by Member States are addressed in this document. WHO will expand on this foundation and provide guidance on other priority areas in future documents.

## Terminology

The definitions given below apply to the terms as used in this WHO document. These terms may have different meanings in other contexts, or in other international or regional regulatory

documents. It should be noted that when reference is made to cells in this document, anucleated cells like red blood cells and platelets are excluded.

**Allogeneic**: referring to cells donated by one person and used to treat another person

**Autologous**: referring to a patient's own cells

**Cell therapy product**: A product composed of human nucleated cells intended for the treatment or prevention of human diseases or physical conditions, through the pharmacological, immunological or metabolic action of its cells or tissues. Isolated substances from the cells such as exosomes are excluded from this definition.

**Combined ATMPs**: ATMPs that include a medical device(s) as an integral part of the product where the device has a role/function in the product's overall effect and is not intended to be removed nor used solely for administration purposes (such as syringes, catheters, etc.).

***Ex vivo* gene therapy product**: Refers to a **gene therapy product** where cells are genetically modified before being given to the patient.

**Gene editing**: The use of guide RNA, which targets a nuclease enzyme to the site in the genome to be cleaved. The most commonly used approaches currently 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) (29).

**Gene therapy product**: A product composed of nucleic acids with the intention to regulate, repair, replace, add or delete a genetic sequence. The intended therapeutic effect is directly linked to the nucleic acid and its use. Gene therapy products include non-viral (plasmids, mRNA, DNA-based) and viral vectors that are used *in vivo* as well as cells that have been modified by such vector's *ex vivo*.

Within this definition, gene edited products are considered as gene therapy products. However, prophylactic vaccines for infectious diseases (e.g., mRNA, plasmid DNA, or viral-vectored vaccines) are excluded from this definition and are not considered to be gene therapy products. It is noted that definitions of gene therapy products may vary between regulatory authorities.

**Homologous use (same essential function/s)**: The concept that the essential functions of the cells or tissues in the recipient are the same, or highly similar, to their functions in the donor. For

example, infusion of bone marrow cells for hematopoietic reconstitution would be considered homologous use. In contrast, use of adipose tissue-derived mesenchymal stromal cells (MSCs) for treatment of osteoarthritis, other musculoskeletal conditions, or diseases of the nervous system, lung, or other non-adipose tissues are considered non-homologous use.

***In vivo* gene therapy product**: Refers to a nucleic acid product (e.g., DNA/RNA, plasmid, virus) administered directly into the patient, and excludes prophylactic vaccines intended to elicit an immune response to prevent infectious diseases.

**Minimal manipulation**: The concept that the cells or tissues do not undergo processing steps that could alter the characteristics, structural properties, functionality or the risk profile of the cells or tissues. Acceptable cell or tissue processing steps might include sizing, rinsing, or washing with solutions such as saline. For example, rinsing a harvested tissue in normal saline to remove debris from the harvested material prior to storage would constitute minimal manipulation. Depending on local legal frameworks, minimal manipulation of cells/tissues also may allow other processing steps such as cutting, grinding, centrifugation, antibiotic treatment, washing, sterilization/irradiation, cell separation, concentration, filtering, cryopreservation etc. However, in all cases, it is expected that such processing does not involve any cell division or altering relevant biological attributes of the cells or tissues.

**Regulatory convergence**: A voluntary alignment of regulatory approaches and requirements across countries and regions as a result of the gradual adoption of international technical guidance documents and standards, and internationally recognized scientific principles, practices, and procedures to achieve a common public health goal.

**Regulatory framework**: The collection of laws, regulations, guidelines, and other regulatory instruments through which a government controls medicinal product manufacturing, clinical evaluation, marketing, promotion and post-market safety monitoring.

**Regulatory harmonization**: A process by which technical guidance documents are developed to achieve uniformed regulatory requirements among participating jurisdictions.

**Tissue engineering product**: A product composed of nucleated human cells that are intended for repair, replacement or regeneration of tissues. Tissue engineered products use cells to form structured tissues, often using natural or artificial scaffolds such as extracellular matrix proteins. Some tissue engineered products may incorporate medical devices.

**Xenogeneic**: referring to cells originating from one species and used to treat individuals of another species.

## Classification of HCTs and ATMPs

Minimal manipulation and homologous use are the concepts that have been embraced by multiple regulatory authorities for making the distinction between HCTs and ATMPs (see clarifications of the definitions in the Terminology section) (2,3,18,20,30). For the purposes of this document, cells and tissues that are harvested and undergo only minimal manipulation (simple processing such as washing or sizing), and which are used to achieve the same essential function/s in the recipient as in the donor (homologous use) are defined as human cells and tissues for medical use or 'HCT'. Cells or tissues that are minimally manipulated fall into a lower risk category and the regulatory requirements focus on ensuring quality and safety of the cells and tissues and the protection of recipients and donors in compliance with the ethical principles (Table 1). The regulations for HCTs primarily aim to prevent possible disease transmission and mitigate risks caused by origin, harvesting and processing of the cells / tissues. When the intention is homologous use of the HCTs, product specific clinical studies are usually not required.

HCTs also provide the starting material for those ATMPs based on cells or tissues, and so need to comply with the regulatory requirements applied to the donation of these materials. The complexities of ATMPs over HCTs arise because they require controlled manufacturing processes with significant manipulation of the cellular or genetic starting material and can include expansion and/or purification steps (Table 1). In addition, their safety and efficacy cannot be predicted without well-controlled studies due to the biological complexity of cells and tissues, and since their structure and/or function may be changed by the manipulation and the production processes. Therefore, ATMPs require comprehensive regulation and demonstration of safety and efficacy with robust data to show good product quality, biological activity (22) and manufacturing consistency prior to marketing authorization (see currently available guidance for ATMPs in the Appendix). In addition, the regulations for ATMPs based on replicating viral vectors and oncolytic viruses should include separate considerations to address the potential for their release into the environment and induction of viral disease in, or transmission to, third parties. Strategies need to be in place to mitigate the risk of such an occurrence; therefore, products consisting of, or containing, replicating viral vectors should be subject to an environmental assessment to evaluate the potential adverse effects that could occur if the viral vector is released into the environment.

It should also be noted that the risk profiles of HCTs and ATMPs are not always clear or easy to address. For example: the use of fresh vs. frozen cells/tissues may have significant impact on the outcome of the treatment; or the risks of using a vector can differ depending on whether it is used *in vivo* or for *ex vivo* transduction. The risk identification should also take into account the level of knowledge (e.g., biology of cells and tissues and their normal functionality), paying special attention to products used for the first time, and where there is limited or no knowledge of their safety or efficacy in humans.

The wide range of products with varying risk profiles that constitute ATMPs requires consideration in their regulation as a class overall. Due to the substantial manipulation required for most ATMPs, controlled manufacturing processes are required to ensure both product consistency and quality. This includes assurance of product identity, purity, biological activity, and freedom from adventitious agents (e.g., viruses or TSE). Therefore, an important aspect in the development of ATMPs is the identification of critical quality attributes (CQAs) for each product. CQAs consist of physical, chemical, biological, and/or microbiological properties or characteristic(s) of a product that should be within an appropriate limit, range, or distribution to ensure the desired product quality. An example of a CQA could be a specific cell surface marker, determined by a methodology such as flow cytometry, that should be present on a minimum percentage of a certain cell type in the product. Ideally, CQAs would correlate with clinical outcome, although this is not always possible or feasible as ATMPs are most likely to have multiple CQAs.

Long-term safety and efficacy follow-up of individuals treated with ATMPs can present challenges because these products may exert long-term effects following even a single administration. For example, Lentivirus vector-transduced CD34+ cells that are systemically administered to correct a genetic defect could exert their effect for years through the integrated presence of the vector in cells. Thus, the risk of insertional mutagenesis should be addressed in non-clinical and clinical studies and the safety surveillance monitoring systems that allow longer term follow-up of all treated patients should be in place to identify any emerging serious adverse events, including the development of malignancy (31). The duration of such safety surveillance needs to be carefully considered to ensure the optimal collection of events without being unduly burdensome for the patients receiving the gene therapy products.

## Regulatory expectations of HCTs and ATMPs

Working towards global convergence on regulatory expectations for HCTs and ATMPs, and ultimately regulatory harmonization, will facilitate global access to these potentially transformative products. Harmonization of regulations and regulatory expectations is a key to

supporting timely product development and access, in part, because it allows product developers to submit regulatory applications more efficiently and cost-effectively across different jurisdictions.

As an initial step towards convergence, it is useful to consider cell-, tissue- and gene-based therapies and products as being in one of two broad categories based on their risks from processing or manufacturing:

1. HCTs where the minimal processing of the cells or tissues places them in a lower risk category and do not usually require pre-market approval, or;
2. ATMPs which require complex manufacturing steps or are composed of cells not being used for the same essential functions, fall into a higher risk category and require pre-market authorization.

This determination is made by addressing some fundamental questions:

- is the product a gene therapy?
- does the product contain nucleated cells?
- is the product minimally manipulated? and
- is the product intended for homologous use?

Application of these questions in classifying these products is shown schematically in Figure 1.

HCTs do not usually require marketing authorization but their donation, processing and transplantation generally must be authorized by competent authorities to ensure their quality, safety as well as the protection of donors and recipients. In addition, the facilities and establishments dedicated to the procurement and processing of HCTs may also require approval/licensing by competent authorities. The use of HCTs for the treatment of diseases or physiological conditions may require approval from a local or institutional ethics committee and often the information on effectiveness of the treatment is collected through clinical studies and/or registries.

For ATMPs across a spectrum of complexities and risks (see Table 1), regulations with stringent requirements on product quality, safety and efficacy, and assuring manufacturing consistency have been established in many jurisdictions. For those countries developing regulatory frameworks for HCTs and ATMPs, it is strongly recommended to ensure the regulations are aligned with any other relevant regulations that may already be established in the jurisdiction, such as those for medical devices.

## A risk-based approach for the regulatory oversight of HCTs and ATMPs

Although HCTs and ATMPs have the potential to bring tremendous benefit to individuals in medical need, they also have the potential to cause serious harm if not prepared and used properly, or not supported by adequate data. For ATMPs in particular, developers may benefit from seeking regulatory guidance before initiating clinical studies to ensure the risks are identified and appropriately mitigated. There needs to be careful consideration of product development and deployment under appropriate regulatory oversight. The maturity of the regulatory systems for oversight of HCTs and ATMPs varies widely among high-, middle-, and low-income countries. The conduct of investigational studies or deployment of these products, especially ATMPs, without appropriate regulatory oversight and adequate safety monitoring can result in severe adverse outcomes for recipients. Similarly, a failure to ensure the containment of ATMPs manufactured with replicating viral vectors could pose a risk to third parties and/or to the environment. Thus, regardless of the regulatory experience and maturity level, it is critical for all regulatory authorities to be familiar with the potential risks and regulatory considerations for HCTs and ATMPs, and the appropriate level of regulation required in each case. This is essential to prevent patients from getting treatments and therapies that have no proven benefit and to ensure their authorization by a competent regulatory authority that has evaluated the product's quality, safety, and efficacy.

A scientifically sound, risk-based approach is a practical way to regulate HCTs and ATMPs and has been adopted in most of the existing national and international guidelines. A risk-based approach is built on identifying the various risks and risk-factors that may impact quality, safety and efficacy of the product, taking into consideration risk factors that may be inherent to the HCT or ATMP, and assuring those risks are mitigated. Since HCTs and many ATMPs are derived or prepared from living organisms or are themselves living organisms, the risk of infectious disease transmission is a fundamental concern and must be mitigated. Additional potential risks can vary and are largely dependent on the cells or tissues, or ATMP type. These may include, for example, the need for appropriate HLA matching in certain transplants and applications, and considerations on the potential immunogenicity, tumorigenicity, genotoxicity, and integrational mutagenesis potential of the product.

Manipulation of cells and tissues can increase the risks of their transformation and tumorigenicity, but also of unwanted immunogenicity and other severe toxicities (32,33). Many gene therapy products are manufactured using recombinant forms of common viruses, which as wild type viruses can be human pathogens. Therefore, gene therapy vectors are usually

constructed so they do not contain the parts of their native genomes that make them pathogenic or allow them to replicate. However, there remains other risks associated with gene therapy products, including replication competent virus contaminants, undesired immunogenicity and insertional mutagenesis leading to tumourigenicity. Good manufacturing practices, proper analytical testing, and adequate non-clinical and clinical studies are required to identify and mitigate as many of the risks as possible to ensure patient safety.

For cells and tissues destined for allogeneic transplantation, it is critical that proper measures are in place to screen the donors of cells and tissues (either living or deceased/cadaveric) for potential infectious diseases, and to conduct appropriate testing of the cells or tissues for the most relevant infectious agents that might be associated with disease transmission to the recipient. These tests generally include those for certain viruses, such as hepatitis B, hepatitis C, and human immunodeficiency virus (HIV), as well as other infectious agents that may be locally or globally relevant.

The entities that collect and distribute HCTs are generally registered by the regulatory authority overseeing them. Registration involves at minimum collection of the name and physical location of the establishment providing the HCTs, as well as a detailed list of the different cells or tissues being offered by the establishment. In addition, there should be verification that the collection, processing and medical use of the HCTs do not pose other risks and that the HCTs offered do not meet the criteria of ATMPs that would require authorization as medical products. This facilitates implementation of systems for tracing products from donor to recipient, which will be important if an infectious agent is identified or suspected in either the donor or recipient of the HCTs. It also facilitates the ability to recall entire lots or classes of products in a timely manner, in the event issues such as bacterial or viral contamination are identified.

ATMPs require the same risk-based approach as HCTs to prevent the transmission of infectious diseases and the mitigation of any other potential risks which may be inherent in the product. In addition, ATMPs require compliance with other key regulatory practices including:

- **Good Manufacturing Practices (GMP)** to ensure that the ATMPs used for clinical trials and commercial production are manufactured under a quality management system with appropriate quality controls, including product comparability assessments following process changes;
- **Good Laboratory Practices (GLP)** are used where possible in safety and other non-clinical studies used to generate pharmacodynamic (PD), pharmacokinetic (PK), biodistribution and safety data for the products to ensure the risks are understood and mitigated before use in humans;

- **Good Clinical Practices (GCP)** are applied to all clinical studies with proper design and control to ensure the collection of robust and reliable safety and efficacy data for the products and appropriate long-term follow-up of the patients.

These aspects require that the regulatory authorities must have the capacity and expertise to evaluate and authorize clinical trial applications, marketing authorization applications and oversee post-marketing surveillance to monitor long-term safety and efficacy of the authorized ATMPs. In addition, the GXP quality systems require the skill and capacity by the regulatory authority and/or its inspectorate to perform necessary inspections to ensure compliance with GMP, GLP, and GCP.

## Considerations in the development of a regulatory framework

The diversity of HCTs and ATMPs may require tailoring of the regulatory framework to adapt to the range of products that a country may authorize for use within its jurisdiction. Use of HCTs that do not require premarket authorization can potentially be administered in settings with less experienced regulatory systems as long as the appropriate regulations are in place to ensure that transmission of infectious diseases is minimized, donor rights and ethical issues are controlled, the HCTs are of appropriate quality and safety factors have been considered for the intended use. It also is important to ensure that mechanisms are in place for both ethical and inspectional oversight and so the products can be traced and recalled if necessary. Under those circumstances, countries can potentially authorize the use of HCTs even in situations where there may be limited resources.

Several options exist for the oversight of ATMPs which due to their risks, manufacturing complexity and intended use, require clinical trials and demonstration of safety and efficacy before authorization for use. For jurisdictions with minimal experience in the regulation of ATMPs and with less well-developed safety surveillance systems, it could be possible to have cell therapy or tissue engineered products marketed following a review process that leads to local approval (e.g., at the regional level) based on sufficient data. Jurisdictions with limited resources and experience with ATMPs also could rely on review assessments from jurisdictions with greater experience in regulating ATMPs. For jurisdictions that already have some experience with cell therapy and tissue engineering products and have an adequate safety surveillance system in place, it may be feasible to review and approve less complex ATMPs that do not have significant risks. For jurisdictions with more extensive experience with the approval of simple ATMPs and which have established safety surveillance systems, it may be reasonable to allow the investigational use of these products in clinical trials locally under an appropriate regulatory framework and with ethics committee oversight. These regulatory authorities may also review

marketing applications for those ATMPs and make decisions regarding approval. There are intermediate states between these various options that a jurisdiction could consider.

## Collaboration and strengthening regulatory capacity globally for oversight of HCTs and ATMPs

Depending on the maturity level of the regulatory authority and its expertise and available resources, it may benefit from collaborating with a more experienced regulatory authority. WHO encourages regulatory cooperation and reliance between authorities and other entities that have a role in the oversight of HCTs and ATMPs. Existing opportunities for joint reviews and inspections, agency visits, collaboration for review of products for rare/ultrarare diseases, regulatory actions based on reliance etc. could be further expanded. Sharing of knowledge, expertise, and experience is crucial for strengthening global regulatory capacity for oversight of HCTs and ATMPs in all regions of the world.

To increase access to quality-assured, safe and effective ATMPs, collaboration between regulators regionally and globally is encouraged to leverage their resources more efficiently. Convergence of regulatory requirements in different jurisdictions increases efficiencies and promotes opportunities for reliance. Such regulatory reliance is even more critical for promoting access to ATMPs since presently, regulators in many countries have limited or no experience with authorization of these products.

Collaboration among regulators currently takes place through regulatory networks that promote cooperation for carrying out various regulatory functions for medical products. For example, the African Vaccine Regulatory Forum (AVAREF) is a platform that brings together regulators from the region to conduct joint reviews of clinical trial applications (34). The WHO collaborative registration procedure (CRP) facilitates the marketing authorization of WHO-prequalified medical products approved by a stringent regulatory authority. ASEAN member states have developed the ASEAN Joint Assessment Procedure for marketing authorizations (35). The Access consortium brings together regulators from five countries to conduct joint reviews of regulatory applications for medical products (36). For exchanges and sharing pharmacovigilance data, WHO member states benefit from the safety information of medical products from the WHO database (37). PIC/S increases mutual confidence in GMP inspections among member countries. Such networks can also be used to promote collaboration for review, authorization, and regulatory oversight of cell and gene therapy products.

## Conclusion and next steps

As more jurisdictions deploy HCTs and ATMPs for use in their populations, it is important that the dialogue among regulators continues in order to promote the global alignment of regulatory requirements. These collaborations and exchanges can be facilitated by the WHO as well as through other international organizations such as the Asian-Pacific Economic Co-operation (APEC) (38) and the International Pharmaceutical Regulators Programme (IPRP) (39), with the goal of further regulatory convergence and ultimately harmonization.

Five key priorities had been identified by Member States to strengthen regulatory capacity for oversight of cell and gene therapies and advance global convergence on the regulation of HCTs and ATMPs. This document is a step towards addressing those priorities through the provision of definitions for key terms relevant to cell and gene therapies, the categorization of HCTs and ATMPs, describing key elements that are important for establishing an effective regulatory framework, and provision of an annotated bibliography with key references and resources that are relevant to the manufacture, development and regulation of cell and gene therapies. To build on the fundamental concepts outlined in this document, the WHO will work to identify key issues in the areas of HCTs and ATMPs across its Member States in order to prioritize the development of specific guidance documents and case studies that can facilitate expanding the knowledge base and sharing of best practices among regulators.

The growing number of authorized cell and gene therapies is a testament to the potential these products have in addressing unmet medical needs for a wide range of diseases or to improve on existing treatments. Scientific knowledge and technology in this field is advancing rapidly and regulators can expect to receive increasing numbers of submissions for complex and novel cell and gene therapy products in the future. Establishing effective regulatory frameworks and investing in strengthening regulatory capacity for oversight of cell and gene therapies will be crucial for assuring their safety and efficacy for use in the population. Global alignment on the regulatory requirements for HCTs and ATMPs is critical for promoting their efficient development, timely authorization in different jurisdictions, and ensuring a more equitable access in all regions of the world.

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Administration, USA; I. G. Reischl, Federal Office for Safety in Health Care, Austria; I. Knezevic and S.H. Yoo, World Health Organization, Switzerland.

Based on the outcome of that working group meeting, the preliminary draft was prepared by P. Marks and G. Raychaudhuri, United States Food and Drug Administration, USA; I. Knezevic and S.H. Yoo, World Health Organization, Switzerland. The preliminary draft was then subject to review by the Working Group and C. A. Bravery, Consultant, the United Kingdom; I. U. Oh, Ministry of Food and Drug Safety, the Republic of Korea; P. Salmikangas, Consultant, Finland; J. Wang, National Institutes for Food and Drug Control, People's Republic of China. Considering the feedback from the Working Group, the resulting first draft was posted on the WHO Biologicals website from 20 December 2021 to 24 January 2022 for a first public consultation.

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# Appendix

## Useful Information for Cell and Gene Therapy Products Regulation

Currently, international initiatives are actively working on information sharing and international convergence for Cell and Gene Therapy Product regulation. Examples of such information for manufacturers and regulators of CGTPs include, but are not limited to:

- IPRP, International Regulatory Frameworks for Cell and Gene Therapies (2021): https://admin.iprp.global/sites/default/files/2021-09/IPRP_CTWG-GTWG_Frameworks_2021_0811_0.pdf

  IPRP Cell Therapy and Gene Therapy Working Groups share regulatory frameworks and guidelines on ATMPs among member jurisdictions to assist manufacturers in accessing global regulatory requirements. Full information on regulations and guidelines can be accessed by the weblink for specific jurisdictions.

- PIC/S, PIC/S GMP Guide Annex 2A (Manufacture of Advanced Therapy Medicinal Products for Human Use): https://picscheme.org/docview/2231

  PIC/S provides specific GMP requirements to ATMP as an annex 2A in the GMP guideline. The annex is divided into two parts. Part A covers specific considerations in ATMP manufacturing, from process of control over seed lots and cell banks to finishing activities and testing. Part B encompasses considerations on particular product types, such as gene therapy products.

- ICH, Nonclinical biodistribution considerations for gene therapy products: https://www.ich.org/page/public-consultations

  ICH provides guidance on nonclinical biodistribution (BD) studies in the development of gene therapy products. This document covers the design of nonclinical BD studies and considerations for interpretation and application of the BD data to support the design of clinical trials.

- WHO, INN Nomenclature Scheme for Cell Therapy Products (2015): https://www.who.int/teams/health-product-and-policy-standards/inn/inn-bio/inn-bio-ct&publication=inn-13-323-4; Mandatory information for INN selection and publication for cell-based therapies including cell-based gene therapy substances (2020), https://www.who.int/teams/health-product-and-policy-standards/inn/inn-bio/inn-bio-ct&publication=inn-20-478

  During the 61st INN Consultation in 2015, a USAN-INN-harmonized nomenclature scheme for cell therapy products was formally finalized and approved by the members of the INN Expert Group designated to deal with the selection of international nonproprietary names. Mandatory information for INN selection and publication for cell-based therapies including cell-based gene therapy substances is available to the applicant for new INN request submissions.

- WHO, Human genome editing: recommendations (2021): https://www.who.int/publications/i/item/9789240030381; Human genome editing: a framework for governance (2021), https://www.who.int/publications/i/item/9789240030060; Human genome editing: position paper (2021), https://www.who.int/publications/i/item/9789240030404

  WHO provides recommendations on the governance and oversight of human genome editing in nine areas, including human genome editing registries. WHO also provides a new governance framework that identifies specific tools, institutions and scenarios to illustrate practical challenges in implementing, regulating and overseeing research into the human genome.

- WHO, Principles on the donation and management of blood, blood components and other medical products of human origin (2017): https://apps.who.int/iris/bitstream/handle/10665/274793/A70_19-en.pdf?sequence=1&isAllowed=y

  WHO recommends ten principles for promoting ethical practices in the donation and management of medical products of human origin, including voluntary consent of the donor, safety, quality and efficacy of donation and provides key considerations for implementation.

- NIBSC, WHO 1st Reference Reagent for Lentiviral Vector Integration Site Analysis https://www.nibsc.org/documents/ifu/18-144.pdf; 1st WHO International Reference Reagent CD4 T-cells (human), https://www.nibsc.org/documents/ifu/15-270.pdf

  NIBSC distributes WHO international measurement standards for assuring the quality of biological medicines. Two WHO international measurement standards are available for cell and gene therapy products. WHO 1st Reference Reagent for Lentiviral Vector Integration Site Analysis is suitable as a qualitative Reference Reagent for lentiviral vector integration site analysis, with a confident detection of the ten defined lentiviral vector integration sites. 1st WHO International Reference Reagent CD4 T-cells (human) are intended for use as a cellular control for CD4 T cell enumeration by flow cytometry.

**Table 1. Examples of HCTs and ATMPs demonstrating the broad range of product complexity and primary potential risks of concern.**

| Product class | Product type | Processing | Indication | Potential clinical risks |
|---|---|---|---|---|
| *Lower risk category* | | | | |
| HCT | Autologous bone marrow cells | Collection of the bone marrow | Hematopoietic reconstitution | Infection |
| HCT | Allogeneic amniotic membrane | Collection and freeze drying, sizing | Treatment of ocular wounds | Infection, immunogenicity |
| HCT | Allogeneic virus-specific T cells, non-engineered | Collection, selection, washing and freezing of selected T cells (no culture and/or expansion) | Treatment of severe infections | Infection, immunogenicity |
| *Higher risk category* | | | | |
| ATMP/CTP* | Autologous PBMCs | Collection, isolation and expansion of the cells, washing and formulation | Treatment of cardiac infarction | Infection, altered reactogenicity |
| ATMP/TEP | Autologous cultured chondrocytes | Collection, expansion, formulation | Cartilage repair | Poor, non-hyaline cartilage |
| ATMP/GTP *in vivo* | Adeno-associated virus + SMN1 gene | Most viral genes replaced by the SMN1 cassette, virus expansion, purification, formulation | Treatment of spinal muscular atrophy | Viral infection, immunogenicity |
| ATMP/CTP | Allogeneic pluripotent stem cells (iPSC / hESC) | Collection, purification, expansion, differentiation, formulation | Treatment of retinitis pigmentosa | Immunogenicity, tumorigenicity |
| ATMP/GTP *ex vivo* | Lentivirus + globin gene in autologous CD34+ cells | Lentivirus vector production using plasmids, purification and transduction into patient CD34+ cells, cell expansion and formulation | Treatment of beta-thalassemia | Integrational mutagenesis, oncogenesis, viral infection |
| ATMP/GTP *ex vivo* | Allogeneic CD19 CAR T cells | Construction of the CAR into lentivirus vector, removal of HLA genes from the T cells with gene editing, expansion, formulation | Hematopoietic malignancies, off-the-shelf | Genotoxicity, immunotoxicity, off-target editing, integrational mutagenesis, neurotoxicity |

*Abbreviations: CAR = chimeric antigen receptor; CTP = cell therapy product; GTP = gene therapy product; hESC = human embryonic stem cells; HLA = human leukocyte antigen; iPSC = induced pluripotent stem cells; PBMCs = peripheral blood mononuclear cells

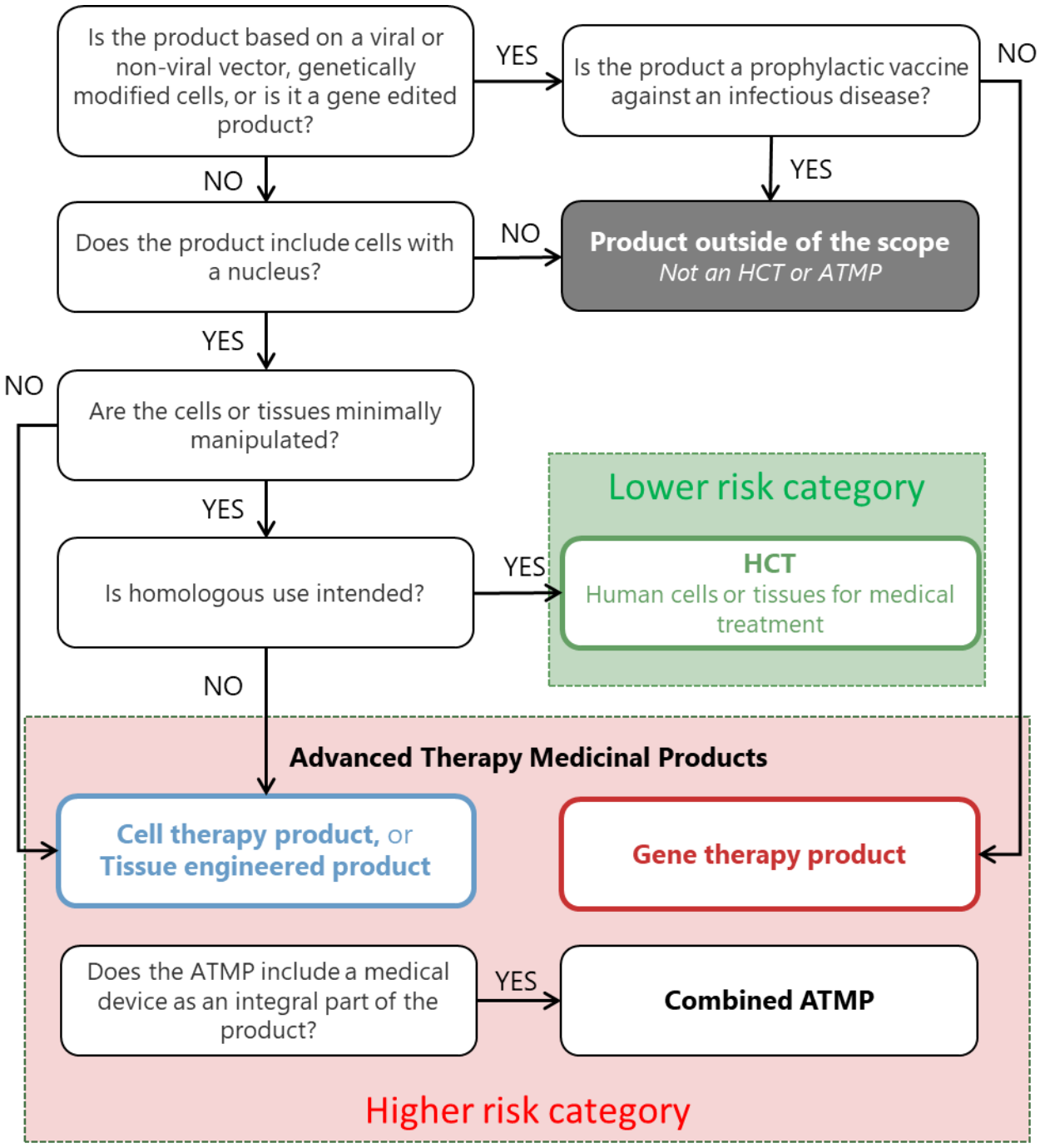


**Figure 1:** A general schema proposed for the regulatory path based on risk category and classification of the HCTs and ATMPs. ATMPs can be subcategorized according to their degree of processing and their mode of application, factors that directly impact risks associated with their use.