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Considerations in developing a regulatory framework for human cells and tissues and for advanced therapy medicinal products

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Annex 3

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Guidance documents published by the World Health Organization (WHO) are intended to be scientific and advisory in nature. Each of the following sections constitutes regulatory considerations for national regulatory authorities (NRAs).

Abbreviations

ATMP	advanced therapy medicinal product
CQA	critical quality attribute
DNA	deoxyribonucleic acid
GCP	good clinical practices
GLP	good laboratory practices
GMP	good manufacturing practices
HCTs	human cells and tissues for medicinal use
ICDRA	International Conference of Drug Regulatory Authorities
mRNA	messenger RNA
NRA	national regulatory authority
RNA	ribonucleic acid

1. Introduction

The use of cell, tissue and gene therapy products for the treatment of human diseases or physical conditions has generated wide interest due to their potential in addressing unmet medical needs. This very broad and diverse class of medicinal products *(1–3)* exhibits levels of complexity ranging from products that have been minimally manipulated prior to administration (such as unprocessed autologous cells and tissue grafts) to those that have undergone significant processing, culturing and/or other manipulation (such as substantially manipulated and/or genetically modified cells). Many countries have now established effective legal frameworks and regulations to protect donors and ensure outcomes in treated patients. Such frameworks and regulations reflect the diversity and complexity of this class of therapeutic product in terms of both product safety and efficacy.

Human cells and tissues which have undergone minimal manipulation are often used to provide the same essential functions in the recipient as they do in the donor, and are defined in this document as human cells and tissues for medicinal use (HCTs). Examples of HCTs include haematopoietic stem cells for the treatment of haematological malignancies, corneas to restore sight and skin grafts to treat burns. Such HCTs may be derived from living donors (for example, haematopoietic stem cells) or from the deceased (for example, heart valves, corneas and skin grafts). With advances in medicine, the number and variety of HCTs are steadily increasing. HCTs are most often regulated within transfusion or transplantation frameworks in which ethical principles and regulatory oversight are established to protect living donors, ensure the quality and safety of the donated material and improve outcomes for transplant recipients through best clinical practices and traceability *(4–6)*.

Advanced therapy medicinal products (ATMPs) for human use are defined as cell and gene therapy products and tissue engineered products that are substantially manipulated and/or perform different functions in the recipient than in the donor. Although typically produced from substantially manipulated or genetically modified somatic cells or tissues, ATMPs can also include nucleic acids, and viral and non-viral vectors, as well as recombinant bacterial cells and recombinant oncolytic viruses *(7–9)*. ATMPs are also very diverse and can include expanded autologous or allogeneic cells, engineered organs, viral products, genetically modified cells, and novel gene editing and/or edited products *(8–11)* (see Appendix 1). ATMPs may also be combined with medical devices, scaffolds or matrices as an integral part of the product ("combined ATMPs"). This wide variety of product types means that ATMPs have the potential to address a broad range of clinical indications, and may have inherent advantages over some existing treatments and current standards of care. Some of these products are rapidly emerging as treatments that provide long-term benefits, potentially transforming the management of diseases such as thalassaemia, sickle cell disease, haemophilia, spinal muscular atrophy, Leber congenital amaurosis, certain cancers, monogenic inherited disorders and many other diseases *(2, 12, 13)*.

ATMPs present unique challenges during their development and production that distinguish them from pharmaceuticals and from other biotherapeutic products. They are also distinguished from HCTs due to their substantial manipulation and/or non-homologous use. As a result, ATMPs can differ from other medicinal products in terms of their manufacturing and quality control requirements, nonclinical assessment, clinical development and post-market monitoring *(8, 9, 14)*. An understanding of these challenges is therefore crucial in the development and establishment of a tenable regulatory framework for the oversight, authorization for marketing and clinical use of such products.

ATMP manufacturing often requires quality-by-design approaches, with additional considerations in their production stemming from the origin, sourcing and limitations of the starting materials (which may include HCTs) and from the manipulation processes that 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 *(9, 15)*. This is particularly the case for genetically modified cells and directly administered vectors or nucleic acids. Therefore, manufacturing facilities for ATMPs are usually separate from the facilities where the starting materials are obtained and processed, and require specific manufacturing authorization by competent medicines authorities for their 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 assessment of the safety and efficacy of ATMPs is challenging for many indications and especially for rare diseases. Such challenges include establishing relevant in vitro systems and/or animal models in which to study product safety and proof-of-concept of its functionality *(16)*. Many associated limitations arise due to inherent differences in the immune systems and physiology of animal species and humans, and the lack of an established animal model of the disease. 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 may also differ between species. Thus, when products are tested across species there are likely to be differences in the responses observed. Similarly, viral vectors may also present their own difficulties when studied using in vitro and/or animal models as they can differ in their tropism and will not necessarily infect all species. Cell-based immunotherapies can also present challenges in their nonclinical assessment due to their exquisite specificity, and to complications such as host-versus-graft responses should human cells be administered to immunocompetent animals. This may be further complicated if the cell-based immunotherapy includes a species-specific genetic modification. Furthermore, the nonclinical testing of therapies which utilize genome editing technologies requires the use of human cells, humanized systems or testing of an animal-adapted version of the product to evaluate potential off-target effects.

Any clinical development programme for HCTs and ATMPs also requires special regulatory consideration as these medicinal products are often being developed for the treatment of rare diseases. Such considerations may include the need to account for the lack of adequately documented natural history data for the disease, 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 there is a limited effect in the overall population and the subgroup of individuals having benefit is not known. Some ATMPs, such as cells harbouring integrated nucleic acids or systemically administered integrating vectors, may have effects that last for years or decades. Under these circumstances, it is important to assess the need for adequate long-term patient follow-up *(17)*.

Countries in all regions of the world are receiving – or have received – clinical trial applications and/or regulatory authorization submissions from companies or non-profit organizations interested in providing access to HCTs and ATMPs. With the growing number of such products and submissions, it is important for regulatory authorities to be aware of the regulatory considerations, challenges and need for adequate supporting data to assure product quality, safety and efficacy, and to avoid unnecessary delays in patient access.

Given the highly varied nature of HCTs and ATMPs, it is not surprising that different national or regional regulatory frameworks have evolved for the oversight of these medicinal products around the world. However, despite their differences, all such frameworks are intended to ensure the highest standards in protecting donors, and ensuring the quality, safety and efficacy of the administered products. Any such regulatory framework should also be based on sound scientific and ethical principles, and include the requirement for comprehensive

evaluation of the benefit–risk ratio applicable to each of the different categories of HCTs and ATMPs.

Effective regulatory decision-making will depend on establishing strong, risk-based regulatory frameworks for the oversight of ATMPs – and of HCTs where these are not sufficiently regulated under an existing transfusion or transplantation framework within a regulatory jurisdiction. Achieving the right balance is crucial – while under-regulation may expose recipients to risk, excessive regulations may deter innovation and hinder access to novel therapies. The key elements of an effective regulatory framework for these types of medicinal product include:

- a clear definition of the categories that constitute HCTs and ATMPs; and
- a risk stratification of the HCTs and ATMPs and a level of regulatory oversight that is appropriate for each category.

In most regulatory jurisdictions with existing legislation and regulations applicable to ATMPs, such products are regulated as medicinal products to ensure their quality, safety and efficacy before authorization for use in the patient population. The regulatory requirements for ATMPs will differ based on stage of product development. As more knowledge is acquired about the product and its safety and efficacy, and as the product moves from investigational to post-authorization use, the requirements will need to be adapted to an appropriate level of stringency, and cover an increasing number of parameters. For HCTs, the regulations will concentrate on the control of possible transmission of communicable diseases and contaminants, as well as on ensuring product quality and safety for its intended use, underpinned by ethical considerations for both the donor and recipient *(4, 5)*. Additionally, the regulatory expectations for ATMPs will also include requirements to address the added risks inherent in such complex, highly manipulated medicinal products *(18–25)*. Furthermore, it will be important to ensure that appropriate long-term post-market surveillance systems are in place, particularly where any adverse reaction to an ATMP may not become evident for many years. In all cases, regulatory decisions should be based on the totality of the available information and on a comprehensive benefit–risk assessment covering the development phase through to the post-authorization phase. Any possible risks which may be introduced as a result of subsequent changes to the production process must also be considered.

As an integral part of their regulatory framework(s), national regulatory authorities (NRAs) with only limited experience of reviewing applications for HCTs and ATMPs, or with limited resources, are encouraged to have mechanisms in place for evidence-based reliance on the assessments and decisions of trusted partners and NRAs with more longstanding experience and expertise in this area. NRAs with limited experience are encouraged to consider the entirety of the product life-cycle (development, licensure and post-market), vigilance, patient access and sustainability when setting up their regulatory framework. This will include any decision-making processes with regard to reliance on the assessments and decisions of more experienced NRAs. The utilization of regulatory reliance for both initial marketing applications and post-approval amendments will help to ensure increased global access to safe and effective HCTs and ATMPs. As NRAs gain experience and expertise, they can consider additional activities (for example, the reviewing of more complex applications in line with their increased capacity and resources) and/or further implement reliance approaches (for example, by participating in work-sharing procedures and/or establishing recognition pathways).

2. Background

In its 2014 resolution WHA67.20, the Sixty-seventh World Health Assembly called for increased WHO support and guidance in strengthening the capacity of countries to regulate increasingly complex biological products, including new medicines based on gene therapy, somatic cell therapy and tissue engineering *(26)*. In addition, the WHO Expert Committee on Biological Standardization has on several occasions highlighted the importance of global-level standardization in the technical and regulatory approaches to these advanced therapies, and the key role of WHO in promoting such standardization *(27–29)*. A consensus was reached by the Committee that global regulatory convergence for advanced medicinal products was needed and that WHO should collaborate with international groups active in this area. As part of this process, the harmonization of definitions and terminology would be particularly helpful for countries now in the process of setting out their own national requirements. Although a variety of relevant guidelines and regulations currently exist or are in development in different regions of the world, the Committee noted during its meeting in October 2021 that there was a high degree of commonality among different NRAs in the ways in which minimally manipulated cells are regulated *(30)*. However, there remained a need to identify common principles for the regulatory evaluation of more complex medicinal products. In addition, during discussion at the 2018 International Conference of Drug Regulatory Authorities (ICDRA), participants noted the potential impact of HCTs and ATMPs on global public health and the need, especially in low- and middle-income countries, to build scientific knowledge and strengthen regulatory capacity to provide oversight of these novel medicinal products. Identified priorities in support of strengthening such regulatory capacity included:

- defining HCTs and ATMPs;
- developing regulatory requirements for HCTs and ATMPs based on sound scientific and risk-based principles; and
- promoting convergence in establishing minimum global standards for ATMPs.

The ICDRA recommendations to WHO were 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. (31).

In response, WHO established an international working group on the standardization of cell and gene therapy products in 2019 to provide expert advice on the development of a WHO considerations document on developing a regulatory framework to assure the quality, safety and effectiveness of these medicinal products. As a first steps in developing the current document the following priorities were identified:

- Provide guidance on the categorization of HCTs and ATMPs, along with definitions of the key terms relevant to this area.
- Summarize the history of ATMPs under development or that have been approved, including examples of the challenges faced in their development, identified solutions and currently unresolved issues.
- Describe the key elements of a regulatory framework that would help to assure the quality, safety and effectiveness of HCTs and ATMPs including:
  - regulatory requirements for different risk categories of products; and

- the need for adequate oversight of these products through their entire life-cycle, including the investigational phase to post-market surveillance, where relevant.
- Develop a proposal on how such a regulatory framework for the various risk categories could be implemented in countries with different levels of regulatory maturity.
- Provide useful information and references to key resources relevant to the development, manufacture and regulation of ATMPs.

3. Purpose and scope

The current document represents a further step in responding to resolution WHA67.20 *(26)*, and to the above recommendations of the WHO Expert Committee on Biological Standardization *(27–29)* and the 2018 ICDRA *(31)*. By outlining a number of fundamental principles and concepts in the regulatory oversight of different types of HCTs and ATMPs, the document is intended to advance and promote both regulatory convergence and the practice of regulatory reliance across all jurisdictions – whether or not adequate regulations are currently in place. It is intended that this will in turn facilitate both the development of and access to advanced medicinal products. The document also outlines a number of priorities in harmonizing regulatory frameworks in order to improve product safety, ensure efficacy, and prevent the exploitation of donors and patients. In this regard, the document also serves to highlight the crucial importance of strengthening national regulatory systems for the oversight of these vitally needed medicinal products.

However, it is also acknowledged that in some countries, many or all HCTs may be regulated within existing regulatory frameworks on transplantation and transfusion. Thus, rather than providing comprehensive guidance on this topic, the current document is instead intended to serve as a foundation for the development of future WHO guidance on assuring the quality, safety and efficacy of HCTs and ATMPs.

The major aspects addressed in this document include:

- provision of definitions for key terms;
- the categorization of HCTs and ATMPs;
- use of a risk-based approach to the regulatory oversight of HCTs and ATMPs;
- the key elements of an effective regulatory framework; and
- provision of useful information on references and resources relevant to the manufacture, development and regulation of HCTs and ATMPs.

It should be noted that definitions of HCTs and ATMPs can vary between countries and regions. For the purposes of this and future WHO regulatory guidance documents in this area, the definitions and terms provided in the **Terminology** section below apply. It should also be noted that germ cells and/or potentially heritable genetic modifications are outside the scope of the current document and of the definitions contained herein. The document also does not apply to xenogeneic products or to organs for transplantation. Similarly, vaccines intended to elicit an immune response against infectious diseases are also outside the scope of this document, and are excluded from the definition of a gene therapy product. A large body of guidance on such prophylactic vaccines already exists and should be consulted instead. However, therapeutic vaccines – such as those under development for the treatment of cancer – fall within the scope of this document. Finally, although ethical principles are a key aspect requiring consideration in any product development process, particularly when donated human materials are involved, this issue is not addressed in the current text.

4. 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 also be noted that in this document, unless otherwise indicated, the term "cells" refers to human cells, excluding anucleated cells such as red blood cells and platelets.

Allogeneic: referring to cells and tissues donated by one person and used to treat a medical condition in another person.

Autologous: referring to cells and tissues taken from, and used to treat a medical condition in, the same person.

Advanced therapy medicinal product (ATMP): 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. **Xenogeneic** cells and tissues are included in the definition of ATMPs but are not within the scope of this document due to the complexity of their application.

Cell therapy product: 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: 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.

Critical quality attribute (CQA): any physical, chemical, biological and/or microbiological property and/or characteristic of a medicinal product that should be within an appropriate limit, range or distribution to ensure the desired product quality.

Gene editing: 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) *(32)*.

Gene therapy product: 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.

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 haematopoietic reconstitution would be considered homologous use, whereas the use of bone-marrow-derived mononucleated cells for the treatment of spinal cord injury, heart failure or osteoarthritis would be considered non-homologous use.

Human cells and tissues for medicinal use (HCTs): human cells and tissues that have undergone minimal manipulation, and which may be used to provide the same essential functions in the recipient as they do in the donor.

In vivo gene therapy product: a gene therapy product administered directly into the recipient.

Minimal manipulation: the concept that cells or tissues do not undergo processing steps that could substantially alter their risk profile (which could include characteristics such as structural properties and functionality), or that could induce their differentiation, activation, proliferation potential or metabolic activity. Minimally manipulated cells and tissues must not have a systemic effect and must depend on their own metabolic activity for their primary function.

> Cell or tissue processing steps that are considered minimal include sizing, rinsing and washing with solutions such as saline. Depending on local legal frameworks, the definition of minimal manipulation may also include other processing steps such as cutting, grinding, centrifugation, freeze-drying, antibiotic treatment, washing, sterilization/irradiation, cell separation or removal, cell suspension, concentration, filtering and/or cryopreservation.

Regulatory convergence: a voluntary alignment of regulatory approaches and requirements across countries and regions that may include the gradual adoption of international technical guidance documents and standards, and internationally recognized scientific principles, practices and procedures.

Regulatory framework: the collection of laws, regulations, guidelines and other regulatory instruments through which a government regulates HCT and ATMP research and development, manufacturing, clinical evaluation, marketing, promotion and post-market safety monitoring, as well as human cell and tissue donation, procurement, testing, processing, preservation, storage, distribution, clinical use, traceability and biovigilance.

Regulatory harmonization: a process by which technical guidance documents are developed to achieve uniform regulatory requirements among participating jurisdictions.

Regulatory reliance: the act whereby a regulatory authority in one jurisdiction may take into account and give significant weight to – that is, totally or partially rely upon – evaluations performed by another regulatory authority or trusted institution in reaching its own decision. The relying authority remains responsible and accountable for the decisions taken, even when it relies upon the decisions and information of others *(33)*.

Tissue engineered product: 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.

Xenogeneic: denoting cells, tissues or organs originating from one species and administered to an individual of another species.

5. Classification of HCTs and ATMPs

Minimal manipulation and homologous use are the concepts that have been embraced by numerous regulatory authorities when distinguishing between HCTs and ATMPs *(4, 7, 8, 24, 34)*. Definitions of these concepts are provided in the Terminology section above, and their application illustrated in Appendices 1 and 2 below. For the purposes of the current document, cells and tissues that are recovered and which 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 they do in the donor (homologous use) are considered to be HCTs. Most minimally manipulated cells and tissues have fewer uncertainties in their risk profile to consider in a risk assessment compared to substantially manipulated cells or tissues. As a result, their regulatory requirements mainly focus on ensuring the quality and safety of the cells and tissues, and on the protection of donors and recipients through compliance with the relevant ethical principles of transplantation frameworks. The quality and safety elements of HCT regulation primarily aim to prevent possible disease transmission and to mitigate risks associated with their origin, or that may arise during cell or tissue procurement and/or processing. When homologous use of human cells and tissues is intended, evidence of their clinical performance must be provided while product-specific clinical studies are usually not required.

Human cells or tissues may also provide the starting material for cell- or tissue-based ATMPs, and thus need to comply with the regulatory requirements applied to the donation, procurement and testing of such cells and/or tissues. The greater complexity of ATMPs compared to HCTs arises because ATMPs usually require controlled manufacturing processes with significant manipulation of the cellular or genetic starting material, and this can include expansion and/or purification steps (Appendix 1). In addition, their safety and efficacy cannot be predicted without well-controlled clinical studies due to the biological complexity of cells and tissues, and because their structure and/or function may be changed by the manipulation and production processes. Depending on the product and disease, clinical studies may require an innovative “fit for purpose” design which considers the complexity of both the ATMP and the treatment. Therefore, ATMPs require comprehensive regulation and demonstration of safety and efficacy, with robust data required to show high product quality, biological activity and manufacturing consistency, both prior to marketing authorization and following any manufacturing process changes *(1, 4, 5, 9, 35)*. Further information on cell and gene therapy product regulation is provided in Appendix 3 below. In addition, regulations for ATMPs based on replicating and non-replicating viral vectors, viable viruses (for example, oncolytic viruses) or other potentially infectious agents which could be shed from the recipient should include separate considerations to address the possibility of their release into the environment, and the resulting induction of disease in (or transmission to) third parties. As strategies need to be in place to mitigate the risk of such an occurrence, this type of product should be subjected to an environmental risk assessment to evaluate the potential adverse effects of their transmission and/or release into the environment.

The wide range of medicinal products of varying risk profiles that constitute ATMPs requires consideration of their regulation as an overall class of product. Due to the substantial manipulation required to produce most ATMPs, controlled manufacturing processes are required to ensure consistency of production and acceptable levels of batch-to-batch variation. This includes assurance of product identity, purity, biological activity and freedom from adventitious agents (for example, viruses and prions) *(36)*. Therefore, an important aspect in the development of ATMPs is the identification of critical quality attributes (CQAs) for each product. Due to the biological complexity of ATMPs, their production control requires multiple CQAs. Ideally, these CQAs would correlate with clinical outcome (such as potency correlating

with product efficacy) – though this may not always be possible or feasible. Examples of potential CQAs include:

- minimum percentage of a certain cell type as determined by specific cell surface markers;
- percent viability of cells;
- in vitro or in vivo potency;
- ratio of full to empty viral capsids; and
- correct genomic sequence.

Long-term safety and efficacy follow-up of individuals treated with ATMPs can also present challenges as 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 nonclinical and clinical studies, and safety surveillance monitoring systems that allow for longer-term follow-up of all treated patients should be in place to identify any emerging serious adverse reactions, including the development of malignancy *(37)*. A risk-based approach should be used to determine the duration of any long-term safety surveillance requirements. Careful consideration is needed to ensure the optimal collection of necessary data without this being unduly burdensome for patients receiving the gene therapy products.

It should also be noted that the risk profiles of HCTs and ATMPs are not always clear, or easy to address, and that HCTs do not necessarily have a lower risk profile than ATMPs. For example, the use of fresh versus frozen cells/tissues may have a significant impact on treatment outcome, while 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 scientific knowledge supporting the use of a medicinal product (for example, on the biology of cells and tissues and their normal functionality) as well as prior manufacturing experience for similar products. Special attention should be paid to medicinal products used for the first time, and/or where there is limited or no knowledge of their safety or efficacy in humans, or experience in their production.

6. Regulatory expectations for HCTs and ATMPs

Working towards the global convergence of regulatory expectations for HCTs and ATMPs, and ultimately regulatory harmonization, will facilitate global access to these potentially transformative medicinal products. The harmonization of regulations and regulatory expectations will be crucial in supporting timely product development and access – in part, because it will allow 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 therapy products as belonging to one of two broad categories based on the risks arising from their processing and/or manufacturing:

1. HCTs – where the minimal processing of the cells or tissues and their intended homologous use introduces fewer uncertainties in their risk profile; or
2. ATMPs – which require complex manufacturing steps or are composed of cells not being used for the same essential functions, thus introducing greater uncertainty in their risk profile.

Such category determinations can be made by answering the following fundamental questions:

- Is the product a gene therapy product and/or does it include genetically modified cells?
- Is the product intended for blood transfusion or organ transplantation?
- Is the product minimally manipulated?
- Is the product intended for homologous use?

A schematic illustration of the application of these questions in classifying HCTs and ATMPs is provided in Appendix 3 below.

Although HCTs do not usually require marketing authorization, their donation, processing and transplantation must generally be authorized by competent authorities to ensure their quality and safety, and to protect 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 also require approval from a local or institutional ethics committee, while information on the effectiveness of the treatment is typically collected through clinical studies and/or registries. Furthermore, any post-approval changes in the processing of HCTs may also require an assessment of associated risks, along with an evaluation of the impact of the change(s) on product specifications and release criteria.

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

7. A risk-based approach to the regulatory oversight of HCTs and ATMPs

Although HCTs and ATMPs have the potential to bring considerable benefits to individuals for a wide range of diseases, they can also cause serious harm if they are not prepared and used properly, or not supported by adequate nonclinical and clinical evidence. Therefore, it is important for regulators to have a good understanding of a product before they approve its use in order to minimize the risk of introducing unproven therapies for which there is an insufficient body of evidence to support clinical use *(38)*. For ATMPs in particular, developers may benefit from early discussions with, and regulatory guidance from, the regulatory authority before initiating clinical studies to ensure that risks are identified and appropriately mitigated. There will need to be careful consideration of product development and deployment under appropriate regulatory oversight. The conducting of investigational studies or deployment of these medicinal products, especially ATMPs, without appropriate regulatory oversight and adequate safety monitoring can result in severe adverse outcomes for product recipients. Similarly, a failure to ensure the containment of ATMPs manufactured using replicating microbial vectors could pose a risk to third parties and/or to the environment. Thus, it is vital that all regulatory authorities are familiar with the potential risks and regulatory considerations for HCTs and ATMPs, and with the appropriate level of regulation required in each case. ATMPs should also be authorized by a competent regulatory authority that has evaluated the product's quality, safety and efficacy. This will be essential in preventing patients from receiving treatments and therapies that have no proven benefit.

A scientifically sound, risk-based approach is a practical way to regulate HCTs and ATMPs and has been adopted in most current national and international guidelines. A risk-based approach involves identifying and taking into consideration all of the various risks and risk factors that may impact product quality, safety and efficacy, including risk factors that may be inherent to the HCTs or ATMP, and ensuring that 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 type of cells or tissues, or ATMP. The mitigation of such risks may include the need for appropriate human leukocyte antigen (HLA) matching in certain transplants and applications, and consideration of the potential immunogenicity, tumorigenicity, genotoxicity, implant failure and insertional mutagenesis of the product.

The manipulation of cells and tissues can increase the risk of their transformation and tumorigenicity, and also of their unwanted immunogenicity and other severe toxicities *(39, 40)*. Many gene therapy products are manufactured using recombinant forms of common viruses, the wild types of which can be human pathogens. Therefore, gene therapy vectors are usually constructed to not contain those parts of their native genomes that make them pathogenic or allow them to replicate. However, other risks associated with gene therapy products remain, including replication-competent virus contaminants, undesired immunogenicity and insertional mutagenesis leading to tumorigenicity. Good manufacturing practices (GMP), good laboratory practices (GLP), and adequate nonclinical and clinical studies conducted under good clinical practices (GCP) are required to identify and mitigate as many risks as possible to ensure patient safety.

For cells and tissues destined for allogeneic transplantation, it is crucial that proper measures are in place to screen the donors (either living or deceased) for relevant communicable disease risks that might be associated with disease transmission from the donor to the recipient. Tests to perform generally include those for certain viruses (such as hepatitis B virus, hepatitis C virus and human immunodeficiency virus) as well as other infectious agents that may be locally or globally relevant. In addition, appropriate testing of the cells or tissues to detect contamination (such as microbiological cultures) should be performed to protect recipients.

The entities that perform donor screening or testing, or that recover, process, store and/or distribute HCTs are generally registered by the regulatory authority overseeing them and should comply with current good tissue practices, where adopted *(41, 42)*. Registration involves, at a minimum, recording 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. This will facilitate the implementation of traceability systems between the donor and recipient, which will be vitally important if an infectious agent is identified or suspected in either the donor or recipient of the HCTs. It will also facilitate the ability to recall entire lots or classes of products in a timely manner should issues such as bacterial or viral contamination be identified. In addition, it should be verified that donor screening and testing, as well as the recovery, processing, storage, distribution and use of the HCTs, do not introduce other risks to the recipients. It should also be verified that the HCTs do not meet the criteria of being ATMPs – in which case they would require specific marketing authorization.

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:

- GMP to ensure that the ATMPs used for clinical trials and clinical use are manufactured under a quality management system with investigational phase-

appropriate quality controls, and procedures in place for the management of process changes.

- GLP applied, where feasible, in required nonclinical studies used to gather safety data for HCTs and ATMPs to ensure that the risks are understood and mitigated before use in humans. Pharmacodynamic (PD), pharmacokinetic (PK) and biodistribution analysis included in a toxicology study is not necessarily required to be conducted under GLP.
- GCP applied to all clinical studies on ATMPs with proper design and control to ensure the collection of robust and reliable safety and efficacy data for the product and appropriate long-term follow-up of patients.

These aspects require that the regulatory authority must have the capacity and expertise to evaluate and authorize both clinical trial and marketing authorization applications, and to oversee post-market surveillance to monitor the long-term safety and efficacy of authorized ATMPs. In addition, ensuring compliance with GMP, GLP and GCP requires that the regulatory authority and/or its inspectorate have the capacities and expertise needed to perform the necessary inspections.

It is essential that the safety of all authorized ATMPs be continually monitored while they are being used in medical practice. This will include the implementation of a pharmacovigilance system for such products in which all authorization holders should participate. To this end, the product authorization holder should have a system for compiling, processing and evaluating information on suspected adverse reactions, and for communicating this information to the regulatory authority. This will enable the early detection of risks and effective mitigation of their consequences for patients, and will inform the design of appropriate post-authorization studies to monitor product safety and efficacy.

8. 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 medicinal products that a country may authorize for use within its jurisdiction. Use of HCTs that do not require marketing authorization can potentially be administered in settings with less experienced regulatory systems. However, appropriate regulations and oversight must be in place to ensure donor rights and safety, and respect for ethical standards to minimize the risk of communicable disease transmission, to ensure that the HCTs are of appropriate quality, and that safety standards (including with regard to coding, traceability and biovigilance) have been appropriately applied for the intended use. It is also important to ensure that mechanisms are put in place for both ethical and inspectional oversight, and that medicinal products can be traced and recalled if necessary.

Due to their risks, manufacturing complexity and intended use, the regulatory oversight of ATMPs requires robust quality assurance mechanisms and the demonstration of safety and efficacy in clinical trials before their authorization for use. Where the necessary experience for such regulatory oversight is not yet in place, several options exist based on the principles of good reliance practices *(33)*. For jurisdictions with minimal experience in the regulation of ATMPs and with less well developed safety surveillance systems, it may be possible to have cell therapy or tissue engineered products marketed following an external regulatory review process by a more experienced regulatory authority. Such an approach would be based both on the external review of the nonclinical and clinical evidence and on the external implementation of appropriate surveillance measures. Jurisdictions with limited resources and experience of ATMPs could also rely on the review and approval of clinical trials and/or marketing applications by jurisdictions with greater experience in regulating ATMPs. For jurisdictions

that already have some experience with cell therapy and tissue engineered products and that have an adequate safety surveillance system in place, it may be feasible to review and approve less complex ATMPs that have had fewer potential risks introduced during their manipulation. For jurisdictions with more extensive experience in the approval of simple ATMPs and which have established safety surveillance systems, it may be reasonable to approve more complex ATMPs and allow their local investigational use in controlled clinical trials under an appropriate regulatory framework and with ethics committee oversight. Such regulatory authorities may also review marketing applications and post-approval changes for these ATMPs and make decisions regarding their approval. There are also intermediate states between these various options that an individual jurisdiction could consider. In general, good reliance practices would also help to minimize the risk of authorizing unproven therapies that have not undergone controlled clinical trials and/or that have an insufficient body of evidence to support their marketing authorization.

9. Collaboration and strengthening global regulatory capacity for the oversight of HCTs and ATMPs

WHO encourages regulatory cooperation and reliance between authorities and other entities involved in the oversight of HCTs and ATMPs. Existing opportunities for joint reviews and inspections, agency visits, collaboration in the reviewing of medicinal products for rare and ultra-rare diseases, regulatory activities based on reliance, and so on could all be further expanded and would positively impact upon the global accessibility of these products. Sharing knowledge, expertise and experience is crucial for strengthening global regulatory capacity for the oversight of HCTs and ATMPs in all regions of the world. For those regulatory authorities now in the process of investing resources in strengthening their regulatory capacity and building up their expertise there would be significant benefits in collaborating with a more experienced regulatory authority. In addition, strengthening regulatory capacity and advancing global convergence in the regulation of HCTs and ATMPs will provide further opportunities for clinical research. This is particularly the case in the field of HCTs and ATMPs intended for the treatment of rare diseases.

To increase access to high-quality, safe and effective ATMPs, collaboration between regulators regionally and globally, including through regulatory networks *(43–46)*, is encouraged to share knowledge and experience and to leverage resources more efficiently. The convergence of regulatory requirements in different jurisdictions will increase efficiencies and promote opportunities for reliance. Such regulatory reliance is even more crucial in promoting access to ATMPs since regulators in many countries currently have limited or no experience in the authorization of these products.

Authors and acknowledgements

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Based on the outcome of the working group meeting, a preliminary first draft was prepared by: P. Marks and G. Raychaudhuri, US FDA, the USA; and I. Knezevic and S.H.

Yoo, World Health Organization, Switzerland. The draft was then subjected to review by the working group and by: C.A. Bravery, consultant, the United Kingdom; I.U. Oh, Ministry of Food and Drug Safety, Republic of Korea; P. Salmikangas, consultant, Finland; and J. Wang, National Institutes for Food and Drug Control, China. Following incorporation of the working group feedback, the resulting document was posted on the WHO Biologicals website from 20 December 2021 to 24 January 2022 for a first round of public consultation.

An informal consultation on the document was then held virtually on 7–9 February 2022 and attended by: *Working group members*; C.A. Bravery, consultant, the United Kingdom; G. Jotwani, Indian Council of Medical Research, India; P. Marks and G. Raychaudhuri, US FDA, the USA; Y. Maruyama, Pharmaceuticals and Medical Devices Agency, Japan; F.C. Melo and R.M. Parca, National Health Surveillance Agency, Brazil; I.U. Oh, Ministry of Food and Drug Safety, Republic of Korea; I.G. Reischl, Federal Office for Safety in Health Care, Austria; P. Salmikangas, consultant, Finland; J. Wang, National Institutes for Food and Drug Control, China; and K. Warre-Cornish, NIBSC, the United Kingdom; *State actors*: J. Arcidiacono, US FDA, the USA; C. Buchholz, Paul-Ehrlich-Institut, Germany; B. Domínguez-Gil, National Transplant Organization, Spain; M.L. Fraga and C. Milne, European Directorate for the Quality of Medicines & Healthcare, France; S. Kellathur and L.L. Ong, Health Sciences Authority, Singapore; M.B.C. Koh, National Blood Bank, Singapore; Z. Park, Ministry of Food and Drug Safety, Republic of Korea; M. Rosu-Myles, Health Canada, Canada; and S. Van Der Spiegel, European Commission; *Observers from non-state actors in official relations*: G. Stacey and J-H. Trouvin, International Alliance of Biological Standardization, Switzerland; *Representation from intergovernmental and other entities*: F. Atouf and J. Jacques, United States Pharmacopeia, the USA; K. Francissen, Roche, the USA; K. Ho, Roche, Switzerland; I. Irony, Janssen, the USA; C. Koerner, Novartis, the USA; K. Nichols, International Society for Cell and Gene Therapy, the USA; G. O'Sullivan, International Society for Cell and Gene Therapy, Australia; K. Quillen, Boston University, the USA; and by C. Ondari, E. Chatzixiros, R.G. Balocco, U. Loizidesi, Y. Maryuningsih, I. Knezevic and S.H. Yoo, World Health Organization, Switzerland.

Based on comments received from the first round of public consultation and the outcomes of the above informal consultation, a second draft of the document was prepared by the working group and by S.H. Yoo and R.A. Isbrucker, World Health Organization, Switzerland. The revised document was posted on the WHO Biologicals website for a second round of public consultation from 5 July to 9 September 2022. The document was also discussed during the October 2022 meeting of the WHO Expert Committee on Biological Standardization and additional revisions proposed for consideration. Based on the comments received during the second round of public consultation and from the Committee, a revised document (WHO/BS/2023.2441) was prepared by R. Isbrucker, World Health Organization, Switzerland, with inputs from: C.A. Bravery, consultant, the United Kingdom; G. Jotwani, Indian Council of Medical Research, India; P. Marks and G. Raychaudhuri, US FDA, the USA; Y. Maruyama, Pharmaceuticals and Medical Devices Agency, Japan; F.C. Melo, National Health Surveillance Agency, Brazil; I.G. Reischl, Federal Office for Safety in Health Care, Austria; and E. Chatzixiros, World Health Organization, Switzerland.

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References

1. Regulation of advanced therapy medicinal products: concept note and recommendations. Ninth Conference of the Pan American Network for Drug Regulatory Harmonization (PANDRH). San Salvador, 24–26 October, 2018.

Washington, DC: Pan American Health Organization; 2019 (https://iris.paho.org/bitstream/handle/10665.2/51558/pahohss19004_eng.pdf?sequence=1&isAllowed=y, accessed 2 May 2023).

2. Wilkins GC, Lanyi K, Inskip A, Ogunbayo OJ, Brhlikova P, Craig D. A pipeline analysis of advanced therapy medicinal products. Drug Discov Today. 2023; 28(5):103549 (https://www.sciencedirect.com/science/article/pii/S135964462300065X, accessed 2 May 2023).

3. El-Kadiry AE, Rafei M, Shammaa R. Cell therapy: types, regulation, and clinical benefits. Front Med (Lausanne). 2021; 8:756029 (https://www.frontiersin.org/articles/10.3389/fmed.2021.756029/full, accessed 2 May 2023).

4. 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. Silver Spring, MD: Food and Drug Administration; 2020 (https://www.fda.gov/media/109176/download, accessed 2 May 2023).

5. Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. Off J L102; 2004:48–58 (https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32004L0023, accessed 2 May 2023).

6. Ashford P, Chapman J, Hildebrandt M, Noël L, Pruett T, Slaper-Cortenbach I et al. Establishing consensus on ethics, traceability and biovigilance for medical products of human origin. Bull World Health Organ. 2021; 99(12):907–9 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8640690/, accessed 2 May 2023).

7. Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. OJ L; 2007:L 324/121–37 (https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32007R1394&from=EN, accessed 3 May 2023).

8. Iglesias-Lopez C, Agusti A, Obach M, Vallano A. Regulatory framework for advanced therapy medicinal products in Europe and United States. Front Pharmacol. 2019; 10:921 (https://www.frontiersin.org/articles/10.3389/fphar.2019.00921/full, accessed 3 May 2023).

9. Goula A, Gkioka V, Michalopoulos E, Katsimpoulas M, Noutsias M, Sarri EF et al. Advanced therapy medicinal products challenges and perspectives in regenerative medicine. J Clin Med Res. 2020: 12(12):780–6 (https://www.jocmr.org/index.php/JOCMR/article/view/3964/25893298, accessed 3 May 2023).

10. Rao M, Mason C, Solomon S. Cell therapy worldwide: an incipient revolution. Regen Med. 2015; 10(2):181–91 (abstract: https://www.futuremedicine.com/doi/10.2217/rme.14.80, accessed 3 May 2023).

11. High KA, Roncarolo MG. Gene therapy. N Engl J Med. 2019;381(5):455–64.

12. Cicalese MP, Aiuti A. New perspectives in gene therapy for inherited disorders. Pediatr Allergy Immunol. 2020;31(Suppl. 24):5–7 (abstract: https://onlinelibrary.wiley.com/doi/abs/10.1111/pai.13149, accessed 11 May 2023).

13. Pinho-Gomes AC, Cairns J. Evaluation of advanced therapy medicinal products by the National Institute for Health and Care Excellence (NICE): an updated review. Pharmacoeconomics - Open. 2022;6(2):147–67 (https://link.springer.com/content/pdf/10.1007/s41669-021-00295-2.pdf, accessed 11 May 2023).

14. Rousseau CF, Mačiulaitis R, Śladowski D, Narayanan G. Cell and gene therapies: European view on challenges in translation and how to address them. Front Med. 2018;5:158 (https://www.frontiersin.org/articles/10.3389/fmed.2018.00158/full, accessed 11 May 2023).

15. Salmikangas P, Menezes-Ferreira M, Reischl I, Tsiftsoglou A, Kyselovic J, Borg JJ et al. Manufacturing, characterization and control of cell-based medicinal products: challenging paradigms toward commercial use. Regen Med. 2015;10(1):65–78 (abstract: https://pubmed.ncbi.nlm.nih.gov/25562353/, accessed 11 May 2023).

16. Preclinical assessment of investigational cellular and gene therapy products. Guidance for industry. U.S. Department of Health and Human Services, Food and Drug Administration; 2013 (https://www.fda.gov/media/87564/download, accessed 10 May 2023).

17. Long term follow-up after administration of human gene therapy products. Guidance for industry. U.S. Department of Health and Human Services, Food and Drug Administration; 2020 (https://www.fda.gov/media/113768/download, accessed 10 May 2023).

18. Commission Directive 2009/120/EC of 14 September 2009 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products. OJ L 2009; 242:3–12 (https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32009L0120, accessed 10 May 2023).

19. Bailey AM, Arcidiacono J, Benton KA, Taraporewala Z, Winitsky S. United States Food and Drug Administration regulation of gene and cell therapies. In: Galli, M., Serabian, M. (eds). Regulatory Aspects of Gene Therapy and Cell Therapy Products. Advances in Experimental Medicine and Biology. Springer, Cham. 2015;871:1–29 (abstract: https://link.springer.com/chapter/10.1007/978-3-319-18618-4_1, accessed 10 May 2023).

20. Maeda D, Yamaguchi T, Ishizuka T, Hirata M, Takekita K, Sato D. Regulatory frameworks for gene and cell therapies in Japan. In: Galli, M., Serabian, M. (eds). Regulatory Aspects of Gene Therapy and Cell Therapy Products. Advances in Experimental Medicine and Biology. Springer, Cham. 2015;871:147–63 (abstract: https://link.springer.com/chapter/10.1007/978-3-319-18618-4_8, accessed 10 May 2023).

21. Ridgway A, Agbanyo F., Wang J, Rosu-Myles M. Regulatory oversight of cell and gene therapy products in Canada. In: Galli, M., Serabian, M. (eds). Regulatory Aspects of Gene Therapy and Cell Therapy Products. Advances in Experimental Medicine and Biology. Springer, Cham. 2015;871:49–71 (abstract: https://link.springer.com/chapter/10.1007/978-3-319-18618-4_3, accessed 10 May 2023).

22. Regenerative medicine [website]. London: Health Research Authority (https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/regenerative-medicine/, accessed 10 May 2023).

23. Choi M, Han E, Lee S, Kim T, Shin W. Regulatory oversight of gene therapy and cell therapy products in Korea. In: Galli, M., Serabian, M. (eds). Regulatory Aspects of Gene Therapy and Cell Therapy Products. Advances in Experimental Medicine and Biology. Springer, Cham. 2015;871:163–79 (abstract: https://link.springer.com/chapter/10.1007/978-3-319-18618-4_9, accessed 11 May 2023).

24. Regulatory overview of cell, tissue or gene therapy products [website]. Singapore: Health Sciences Authority (https://www.hsa.gov.sg/ctgtp/regulatory-overview, accessed 10 May 2023).

25. Lin YC, Wang PY, Tsai SC, Lin CL, Tai HY, Lo CF et al. Regulation of cell and gene therapy medicinal products in Taiwan. In: Galli, M., Serabian, M. (eds). Regulatory Aspects of Gene Therapy and Cell Therapy Products. Advances in Experimental Medicine and Biology. Springer, Cham. 2015;871:181–94 (abstract: https://link.springer.com/chapter/10.1007/978-3-319-18618-4_10, accessed 11 May 2023).

26. Resolution WHA67.20. Regulatory system strengthening for medical products. Sixty-seventh World Health Assembly, Geneva, 24–31 May 2014. Agenda item 15.6. Geneva: World Health Organization; 2014 (https://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_R20-en.pdf, accessed 11 May 2023).

27. Regulation of cell therapy products. In: WHO Expert Committee on Biological Standardization: sixty-seventh report. Geneva: World Health Organization; 2017 (WHO Technical Report Series, No. 1004, section 3.3.1, pp. 36–38; https://www.who.int/publications/i/item/9789241210133, accessed 11 May 2023).

28. Global activities in cell therapy products. In: WHO Expert Committee on Biological Standardization: sixty-eighth report. Geneva: World Health Organization; 2018 (WHO

Technical Report Series, No. 1011, section 3.2.1, pp. 30–31; https://www.who.int/publications/i/item/9789241210201, accessed 11 May 2023).

29. Update on cellular and gene therapies. In: WHO Expert Committee on Biological Standardization: sixty-ninth report. Geneva: World Health Organization; 2019 (WHO Technical Report Series, No. 1016, section 3.3.1, pp. 34–35; https://www.who.int/publications/i/item/9789241210256, accessed 11 May 2023).

30. Standardization of cell and gene therapy products; and WHO white paper on regulatory convergence for CGTPs. In: WHO Expert Committee on Biological Standardization: seventy-fourth report. Geneva: World Health Organization; 2022 (WHO Technical Report Series, No. 1039, sections 3.3.1 and 3.3.2, pp. 31–33; https://www.who.int/publications/i/item/9789240046870, accessed 11 May 2023).

31. 18th International Conference of Drug Regulatory Authorities. WHO Drug Information. 2018; 32(4):517 (https://apps.who.int/iris/bitstream/handle/10665/330900/DI324-509-518-eng.pdf, accessed 11 May 2023).

32. Li H, Yang Y, Hong W, Huang M, Wu M, Zhao X. Applications of genome editing technology in the targeted therapy of human diseases: mechanisms, advances and prospects. Signal Transduct Target Ther. 2020;5(1):1 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6946647/, accessed 11 May 2023).

33. Good reliance practices in the regulation of medical products: high level principles and considerations. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fifth report. Geneva: World Health Organization; 2021: Annex 10 (WHO Technical Report Series, No. 1033; https://apps.who.int/iris/bitstream/handle/10665/340323/9789240020900-eng.pdf, accessed 11 May 2023).

34. International regulatory frameworks for cell and gene therapies. International Pharmaceutical Regulators Programme (IPRP); 11 August 2021 (https://admin.iprp.global/sites/default/files/2021-09/IPRP_CTWG-GTWG_Frameworks_2021_0811_0.pdf, accessed 11 May 2023).

35. The Committee for Advanced Therapies. Challenges with advanced therapy medicinal products and how to meet them. Nat Rev Drug Discov. 2010;9(3):195–201 (abstract: https://www.nature.com/articles/nrd3052, accessed 11 May 2023).

36. Petricciani J, Hayakawa T, Stacey G, Trouvin JH, Knezevic I. Scientific considerations for the regulatory evaluation of cell therapy products. Biologicals. 2017;50:20–6 (https://www.sciencedirect.com/science/article/pii/S1045105617301203?via%3Dihub , accessed 11 May 2023).

37. Reflection paper on management of clinical risks deriving from insertional mutagenesis. London: European Medicines Agency; 2013 (Document EMA/CAT/190186/2012; https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-management-clinical-risks-deriving-insertional-mutagenesis_en.pdf, accessed 11 May 2023).

38. Srivastava A, Mason C, Wagena E, Cuende N, Weiss DJ, Horwitz et al. Part 1: Defining unproven cellular therapies. Cytotherapy. 2016;18(1):117–9 (abstract: https://www.isct-cytotherapy.org/article/S1465-3249(15)01111-1/fulltext, accessed 12 May 2023).

39. Volarevic V, Markovic BS, Gazdic M, Volarevic A, Jovicic N, Arsenijevic N et al. Ethical and safety issues of stem cell-based therapy. Int J Med Sci. 2018;15(1):36–45 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5765738/, accessed 12 May 2023).

40. Anguela XM, High KA. Entering the modern era of gene therapy. Annu Rev Med. 2019;70:273–88 (https://www.annualreviews.org/doi/10.1146/annurev-med-012017-043332?, accessed 12 May 2023).

41. Current good tissue practice (CGTP) and additional requirements for manufacturers of human cells, tissues, and cellular and tissue-based products (HCT/Ps). Guidance for industry. U.S. Department of Health and Human Services, Food and Drug Administration; 2011 (https://www.fda.gov/media/82724/download, accessed 10 May 2023).

42. Good practices for evaluating quality, safety and efficacy of novel tissue and cellular therapies and products. Guidance, methodologies and tools. EUROGTP II Guide. 2019 (http://www.goodtissuepractices.site/docs/EuroGTP_II_Guide.pdf, accessed 12 May 2023).

43. African Vaccine Regulatory Forum (AVAREF) [website]. Brazzaville: WHO Regional Office for Africa (https://www.afro.who.int/health-topics/immunization/avaref, accessed 12 May 2023).

44. ASEAN Joint Assessment Procedure for Pharmaceutical Products. Available at Health Sciences Authority [website]. Singapore: Health Sciences Authority (https://www.hsa.gov.sg/therapeutic-products/international-collaboration/ASEAN-JA, accessed 12 May 2023).

45. Australia-Canada-Singapore-Switzerland-United Kingdom (Access) Consortium. Available at Therapeutic Goods Administration [website]. Woden ACT: Therapeutic Goods Administration (https://www.tga.gov.au/australia-canada-singapore-switzerland-united-kingdom-access-consortium, accessed 12 May 2023).

46. Regulatory system strengthening in the Americas. Lessons learned from the national regulatory authorities of regional reference. Washington (DC): Pan American Health Organization; 2022 (https://iris.paho.org/handle/10665.2/53793, accessed 12 May 2023).

Appendix 1

Examples of HCTs and ATMPs demonstrating the broad range of product complexity and primary potential risks of concern

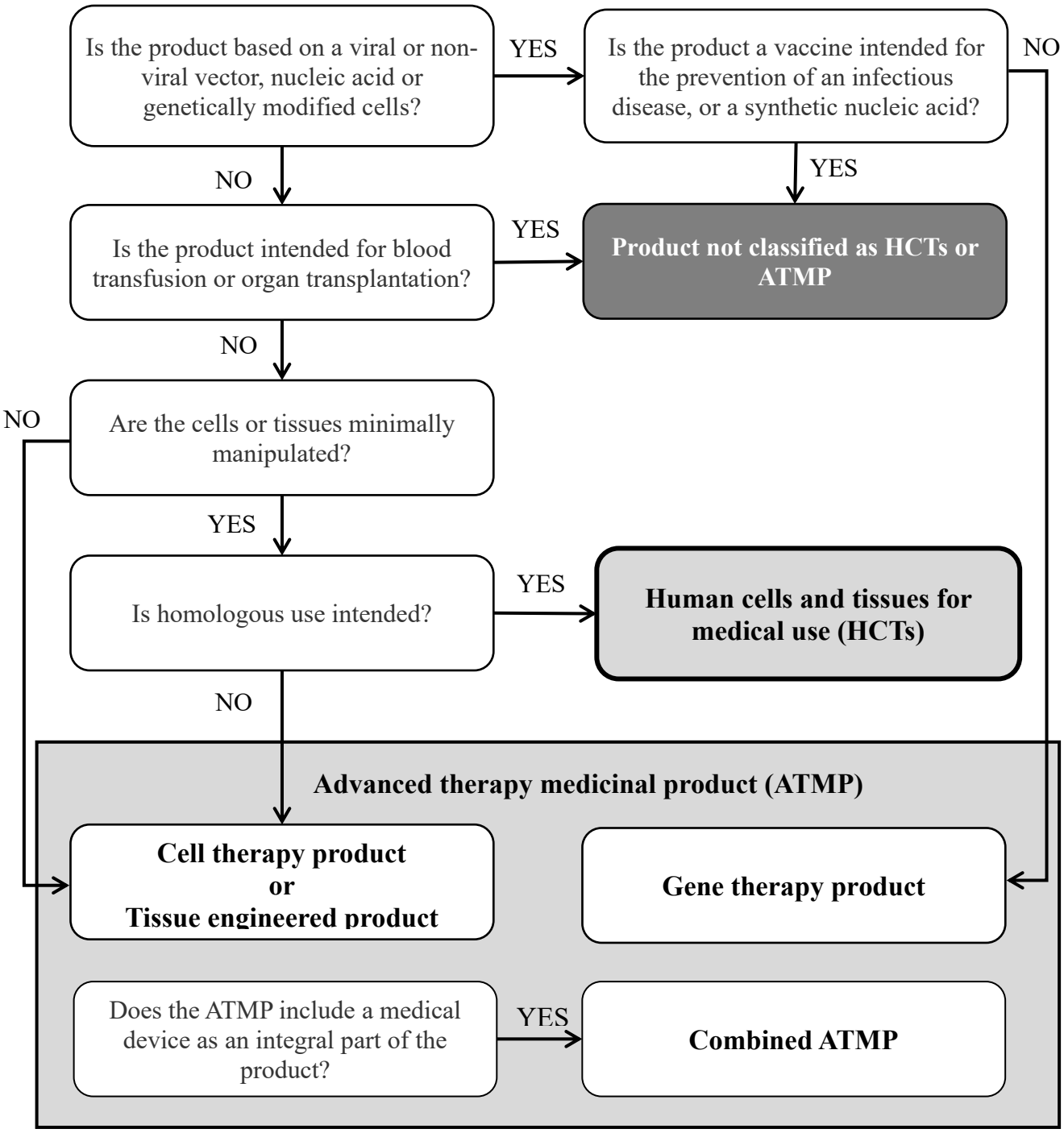
Product class	Product type	Processing	Indication	Potential clinical risks
HCT	Allogeneic bone marrow cells	Collection of the bone marrow	Haematopoietic reconstitution	Infection; graft failure
HCT	Allogeneic amniotic membrane	Collection and freeze drying, sizing	Treatment of ocular wounds	Infection; immunogenicity
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
ATMP/CTP	Autologous PBMCs	Collection, isolation and expansion of the cells, washing, 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; immune-related acute liver failure
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, formulation	Treatment of beta-thalassaemia	Insertional 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 by gene editing, expansion, formulation	Haematopoietic malignancies	Genotoxicity; immunotoxicity; off-target editing; insertional mutagenesis; neurotoxicity

CAR = chimeric antigen receptor; CTP = cell therapy product; GTP = gene therapy product; hESC = human embryonic stem cell; HLA = human leukocyte antigen; iPSC = induced pluripotent stem cell; PBMCs = peripheral blood mononuclear cells; TEP = tissue engineered product.

Appendix 2

Proposed general schema for the classification of HCTs and ATMPs

Note: ATMPs can be subcategorized according to their degree of processing and their mode of application – factors that directly impact upon the risks associated with their use.



Appendix 3

Useful information for cell and gene therapy products regulation

Currently, a number of international initiatives are actively working on promoting information sharing and international convergence with regard to the regulation of cell and gene therapy products. Examples of such information for manufacturers and regulators include, but are not limited to:

- International regulatory frameworks for cell and gene therapies. International Pharmaceutical Regulators Programme (IPRP); 11 August 2021 (https://admin.iprp.global/sites/default/files/2021-09/IPRP_CTWG-GTWG_Frameworks_2021_0811_0.pdf, accessed 28 April 2023).

  The IPRP Cell Therapy and Gene Therapy Working Groups share regulatory frameworks and guidelines on ATMPs provided by participating regulatory authorities to help manufacturers access global regulatory requirements. Links to further information on the laws and regulations in specific jurisdictions are provided in the above document.

- Manufacture of advanced therapy medicinal products for human use. In: Guide to good manufacturing practices for medicinal products; Annex 2A. Geneva: Pharmaceutical Inspection Co-operation Scheme (PIC/S); 2022 (https://picscheme.org/docview/4590, accessed 28 April 2023).

  PIC/S provides specific GMP requirements for ATMPs as Annex 2A in their GMP guideline. The annex is divided into two parts: Part A, covering specific considerations in ATMP manufacturing (from process of control over seed lots and cell banks to finishing activities and testing); and Part B, encompassing considerations of particular product types (such as gene therapy products).

- Nonclinical biodistribution considerations for gene therapy products. S12. ICH Harmonised Guideline. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH); 2023 (Document S12; https://database.ich.org/sites/default/files/ICH_S12_Step4_Guideline_2023_0314.pdf, accessed 28 April 2023).

  ICH Guideline S12 provides guidance on nonclinical biodistribution studies during the development of gene therapy products. The document covers the design of nonclinical biodistribution studies and considerations in the interpretation and application of the resulting data to support the design of clinical trials.

- INN nomenclature scheme for cell therapy products (CTP). Geneva: World Health Organization; 2015 (INN Working Doc. 13.323 revision 4; https://www.who.int/publications/i/item/inn-13-323-4, accessed 28 April 2023); and Mandatory information for INN selection and publication for cell-based therapies including cell-based gene therapy substances. Geneva: World Health Organization; 2020 (INN Working Doc. 20478; https://www.who.int/publications/i/item/inn-20-478, accessed 28 April 2023).

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. The Mandatory information for INN selection and publication for cell-based therapies including cell-based gene therapy substances document is provided as an annex to the INN application form to be used for requesting a new INN.

- Human genome editing: recommendations. Geneva: World Health Organization; 2021 (https://www.who.int/publications/i/item/9789240030381, accessed 28 April 2023); Human genome editing: a framework for governance Geneva: World Health Organization; 2021 (https://www.who.int/publications/i/item/9789240030060, accessed 28 April 2023); and Human genome editing: position paper. Geneva: World Health Organization; 2021 (https://www.who.int/publications/i/item/9789240030404, accessed 28 April 2023).

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

- Principles on the donation and management of blood, blood components and other medical products of human origin. Report of the Secretariat. In: Seventieth World Health Assembly. Provisional agenda item 13.2. 3 April 2017 (Document A70/19: https://apps.who.int/iris/bitstream/handle/10665/274793/A70_19-en.pdf?sequence=1&isAllowed=y, accessed 28 April 2023).

  In this report to the Health Assembly, WHO sets out 10 principles for promoting ethical practices in the donation and management of medical products of human origin, including voluntary consent of the donor, and ensuring the safety, quality and efficacy of donation, while also providing key considerations in the implementation of these principles.

- WHO guiding principles on human cell, tissue and organ transplantation. Geneva: World Health Organization; 2010 (Document number: WHO/HTP/EHT/CPR/2010.01; https://apps.who.int/iris/handle/10665/341814, accessed 28 April 2023).

  WHO recommends 11 guiding principles which are intended to provide an orderly, ethical and acceptable framework for the acquisition and transplantation of human cells, tissues and organs used for therapeutic purposes.

- First WHO International Reference Reagent for lentiviral vector integration site analysis (NIBSC code: 18/144; https://www.nibsc.org/documents/ifu/18-144.pdf, accessed 28 April 2023); and First WHO International Reference Reagent for CD4 T-cells (human) (NIBSC code: 15/270; https://www.nibsc.org/documents/ifu/15-270.pdf, accessed 28 April 2023).

  The UK Medicines and Healthcare products Regulatory Agency (MHRA) distributes WHO international measurement standards for assuring the quality of biological products. The above two WHO international reference reagents are available for cell and gene therapy products. The First WHO International Reference Reagent for lentiviral vector integration site analysis is suitable for use as a qualitative reference material for the detection of the 10 defined lentiviral vector integration sites. The First WHO International

Reference Reagent for CD4 T-cells (human) is intended for use as a cellular control for CD4 T-cell enumeration by flow cytometry.