World Health Organization

WHO/CGTPs/DRAFT/16 December 2021
ENGLISH ONLY

WHO considerations on Regulatory Convergence of 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 to a broad audience and to improve transparency of the consultation process.

The text in its present form does not necessarily represent an agreed formulation of the ECBS. Written comments proposing modifications to this text MUST be received by 24 January 2022 using the Comment Form available separately and should be addressed to: Department of Health Products Policy and Standards (HPS), World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland. Comments may also be submitted electronically to the Responsible Officer: Dr Si Hyung Yoo at yoos@who.int.

The outcome of the deliberations of the ECBS 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 second edition of the *WHO style guide* (KMS/WHP/13.1).

WHO considerations on Regulatory Convergence of Cell and Gene Therapy Products

Introduction 5
Purpose and scope 7
Terminology 8
Definitions 9
Common Regulatory Expectations 12
Application of a Risk-Based Approach 13
References 17
Appendix 21

This document is intended to describe current WHO's thinking on considerations for regulation of Cell and Gene Therapy Products (CGTPs), to promote convergence, and encourage the Member States to strengthen their regulatory system on Cell and Gene Therapy Products regulation. This document is not intended to be a comprehensive overview of regulatory requirements for CGTPs or the different regulatory frameworks that currently exist in different jurisdictions. The objective of this document is to outline the fundamental principles that are important for providing adequate regulatory oversight for different types of CGTPs and should be reviewed in that context. In the future, WHO plans to develop more comprehensive written guidance, as needed, on specific topics relevant to regulation of CGTPs.

Abbreviations

ASEAN	Association of Southeast Asian Nations
ATMP	Advanced Therapy Medicinal Product
AVAREF	African Vaccine Regulatory Forum
CD	Cluster of Differentiation
CGTPs	Cell and Gene Therapy Products
CRP	Collaborative Procedure
CTA	Clinical Trial Application
CTP	Cell Therapy Product
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GTP	Gene Therapy Product
HCT	Human Cells and Tissues for Medical Use
HIV	Human Immunodeficiency Virus
ICDRA	International Conference of Drug Regulatory Authorities
LCA	Leber´s Congenital Amaurosis
LMICs	Low- and Middle-Income Countries
PD	Pharmacodynamic
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PK	Pharmacokinetic
SMA	Spinal Muscular Atrophy
TEP	Tissue Engineered Product
WHO	World Health Organization

Introduction

Use of cells, tissues, and gene therapy products for the treatment of diseases or physiological conditions has become of wide interest due to their potential to address serious unmet medical needs. These cell and gene therapy products (CGTPs) *(1)* encompass a remarkably broad range of complexity, ranging from unprocessed skin grafts (relatively simple) to gene therapies (highly complex). Simple, minimally manipulated cells and tissues are often used for same essential function in the recipient as in the donor (transplantation, transfusion) and are regulated mainly to prevent possible disease transmission (defined here as human cells and tissues for medical use, HCT) *(2,3)*. Advanced therapy medicinal products (ATMPs) consist of cell and gene therapy products and tissue engineering products, which are produced from manipulated cells or tissues, genetic materials or suitable vectors like plasmids or viruses *(3,4)*. ATMP product types are diverse and range from expanded patient cells, to engineered organs, viral products, genetically modified cells and novel gene editing products *(5,6)* (see table 1.). ATMPs can also include medical devices (e.g., scaffolds or matrices) as an integral part of the product; those are called combined ATMPs for which the regulations of devices also may apply. ATMPs have the potential to address a variety of unmet medical needs or may have inherent advantages over existing treatments. They also are emerging rapidly as potentially curative therapies that could transform the management of diseases like thalassemia, sickle cell disease, hemophilia, spinal muscular atrophy (SMA), Leber´s congenital amaurosis (LCA) and many other inherited diseases *(7)*.

ATMPs have unique features that distinguish them from more traditional pharmaceutical products and their development may differ from the traditional path in a variety of areas including non-clinical assessment, manufacturing, clinical development, and post-market monitoring *(8)*. As for many new indications and especially for orphan diseases, the non-clinical testing of ATMPs often can be challenging, in particular for finding appropriate *in vitro* systems or animal models *(9)*. In addition, there are a number of challenges quite unique to ATMPs, like species specificities that may hamper extrapolation of non-clinical results to humans. The specificity of a single human protein for its ligand can limit the animal species in which the product can be evaluated. For cell-based medicines, typically multiple receptor-ligand interactions are involved, and even where compatible the physiological outcome of these interactions can also differ between species. Similarly, viral vectors differ in their tropism and will not necessarily infect all species. Immunotherapies based on cells with or without concurrent genetic modification perhaps pose the greatest challenge in the non-clinical assessments due to the exquisite specificity of the immune system, and in-built mechanisms of host defense. Furthermore, for therapeutic products that utilize genome editing technology, non-clinical testing to evaluate off-target effects generally requires use of human cells.

Manufacturing of ATMPs can be highly complex and require very specialized facilities

and techniques to allow product processing and formulation *(10)*. That is the case especially for genetically modified cells and directly administered gene therapy products *(11)*. Clinical development may present a variety of challenges including the lack of adequately documented natural history for rare diseases as well as the need to evaluate clinical safety and efficacy in very small patient populations *(12)*. Alternatively, interpretation of results from a randomized, controlled clinical trial for some ATMPs may be hampered by small clinical effects and lack of suitable comparators. Finally, since some of these products may have effects that last many years, ensuring adequate patient follow up to facilitate proper post-market surveillance can be challenging *(13)*. For example, systemically administered gene therapy products could potentially have effects that last decades. All together, these factors distinguish ATMPs from more conventional drugs and preventative or therapeutic biologics and require special considerations.

Due in part to the varied nature of CGTPs, it is not surprising that the regulatory frameworks have evolved somewhat differently in Europe, Asia, Australia, North and South America and Africa. However, ATMPs are regulated mostly as medicinal products under existing or specific legislations to ensure quality, safety and efficacy before they are authorized for use in the patient population. The regulatory framework should be based on sound scientific and ethical principles and comprehensive evaluation of risks vs benefits for the different categories of CGTPs. For low risk HCTs the regulations are concentrating on control of possible contaminations and disease transmission *(2,14)*, whereas the regulatory expectations for ATMPs are higher to address the risks of highly manipulated products *(15-22)*. The key elements of a framework include: 1) clear definition of the categories of products that constitute CGTPs, 2) risk stratification of the products defined as CGTPs, 3) aligning the level of regulatory control based on the different risk categories and, 4) consideration of the maturity level, expertise, and resources of the regulatory authority for providing oversight of CGTPs in the different risk categories.

As high-income countries work towards further regulatory convergence for these products, it is important to ensure that regulators in low- and middle-income countries (LMICs) are familiar with the scientific principles and regulatory issues for CGTPs also. Important factors include understanding of the scope (breadth and the nature of HCTs and ATMPs), risks and the key regulatory concepts relevant to ensuring that the more complex products are shown to be safe and effective prior to their widespread deployment. The importance of post-market surveillance systems must also be emphasized to ensure the continued safety and effectiveness of ATMPs, which can have effects that last for many years. A high degree of manipulation of cells and tissues can not only raise the risks of transformation and tumorigenicity, but also of unwanted immunogenicity and other severe toxicities *(23,24)*. Many gene therapy products are produced from common viruses, which as wild type viruses can be human pathogens. Therefore, the gene therapy vectors are usually made so they do not contain the parts of their

native genomes that would allow them to replicate. However, there potentially are high risks associated also with the gene therapy products, spanning from replicating virus contaminants to immunogenicity and tumourigenicity. Proper analytical testing and pre-clinical / clinical studies are required to identify and mitigate as many of the risks as possible to ensure patient safety. It is quite possible that LMICs will start to receive marketing authorization applications from companies or non-profit organizations interested in providing access to these potentially transformative products for diseases that currently are untreatable or inadequately treated in many countries. Preparing regulatory authorities in LMICs to assess the benefits and risks of such ATMPs is critical to avoid unnecessary risks to patients who receive them. Similarly, raising awareness of the challenges, including manufacturing challenges, is critical to avoid unnecessary delays in access to these products.

Purpose and scope

At the 2018 International Conference of Drug Regulatory Authorities (ICDRA) meeting *(25)*, Member States noted the potential impact of CGTPs for global public health and the need, especially in LMICs, to build scientific knowledge and strengthen regulatory capacity to provide oversight of these novel products. The following areas were identified as priorities:

- Defining what CGTPs are (what is in scope and what is out of scope)
- Developing regulatory requirements for CGTPs based on sound science and risk-based principles
- Need for convergence on minimum global standards for ATMP quality

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."

This document is the first step in responding to the 2018 ICDRA recommendation 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 CGTPs, including ATMPs. The priorities are to:

1) Clearly describe what the CGTPs are, describe how the subsets of HCTs and ATMPs are defined from this larger class, and provide definitions of key terminology relevant in this area. Examples will be provided in a subsequent document, as appropriate;

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. These examples should cover nonclinical development, clinical development, and product manufacturing and quality;

3) Provide the key elements of a regulatory framework that supports the safety and effectiveness of CGTPs including suggested regulatory controls for different risk categories of products covering key elements for adequate oversight spanning the entire product lifecycle from the investigational phase through 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. Examples will be provided in a subsequent document, and;

5) Provide an annotated bibliography to highlight key references relevant to the manufacture, product development, and regulation of ATMPs.

The WHO goal is to promote regulatory convergence for CGTPs to facilitate development and access to these novel products for patients in all regions of the world. In addition, the aim is to increase safety of patients treated with CGTPs by preventing exploitation of those jurisdictions with inadequate regulations in place for the safe oversight of such novel products (26,27).

WHO Expert Committee on Biological Standardization (ECBS) recognized that CGTPs have great potential in the treatment of various diseases and would become important future public health interventions (28). The committee had a clear consensus that global harmonization in CGTPs is needed and that WHO should become engaged in this area (28). For this purpose, the committee had recommended that WHO collaborate with other international groups active in the area of CGTPs for harmonizing guidelines (28). WHO had been active in identifying opportunities for collaboration towards regulatory convergence, including collaboration with international groups and initiatives (29,30,31). In line with this effort, this document is intended to describe WHO considerations for regulation of CGTPs, to promote convergence, and encourage the Member States to strengthen their regulatory system on CGTPs regulation.

Terminology

The definitions given below apply to the terms as used in this WHO consideration. These terms may have different meanings in other contexts.

Autologous cell product is manufactured using patients own cells

Allogeneic cell product is manufactured from cells obtained from voluntary donations, often from healthy individuals

Xenogeneic cell product is manufactured using animal cells

Cell therapy product is composed of viable human or animal cells with nucleus, intended for treatment or prevention of human diseases or physiological conditions

Gene therapy product is manufactured from nucleic acids using a recombinant technology. The products include plasmids and viral vectors that may be used in vivo or ex vivo. In addition, gene editing products when fulfilling this definition are gene therapy products. Viral products for infectious diseases are excluded and are not considered to be gene therapy products. Definitions of gene therapy products may vary between regulatory authorities.

Tissue engineering product is composed of viable human or animal cells with nucleus and which are intended for repair or regeneration of tissues.

Combined ATMP are cell or gene therapy products or tissue engineering products that include medical device(s) as an integral part of the product.

Minimal manipulation is the concept that a cell or tissue product does not undergo processing other than certain rudimentary steps that do not alter the characteristics, functionality or the risk profile of the product. 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.

Minimal manipulation may include cutting, grinding, centrifugation, antibiotic treatment, washing, sterilization/irradiation, cell separation, concentration, filtering, cryopreservation, lyophilization, vitrification; enzymatic digestion and short cell incubation are considered minimal manipulation if not involving cell division or altering relevant biological attributes of the cells

Same essential function (homologous use) is the concept that the essential function of the cells or tissues in the recipient should be the same, or highly similar, to the function in the donor. For example, a bone graft from a cadaveric donor that is used to replace bone in the recipient would be considered homologous use.

Definitions

Biological products present unique challenges in manufacturing related to their inherent nature. This is particularly true for those biological products that are CGTPs. Some CGTPs fall into a lower risk category and do not require the same stringency of regulation as more complex products like the ATMPs (Figure 1). For the purposes of this discussion, cells and tissues that are harvested and undergo only simple processing such as washing or sizing (minimal manipulation), 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, HCT. Such cells and tissues are also regulated, but mainly to prevent possible disease transmissions and mitigate risks caused by origin, sourcing and processing of the cells / tissues. HCTs can be used as such for

treatment of patients or utilized as starting materials for ATMP production.

Minimal manipulation and homologous use are regulatory concepts that have been embraced by multiple regulatory authorities for making the distinction between HCTs that present lower risk and ATMPs that present higher risk and which must be regulated more stringently (see clarifications of the definitions in the glossary).

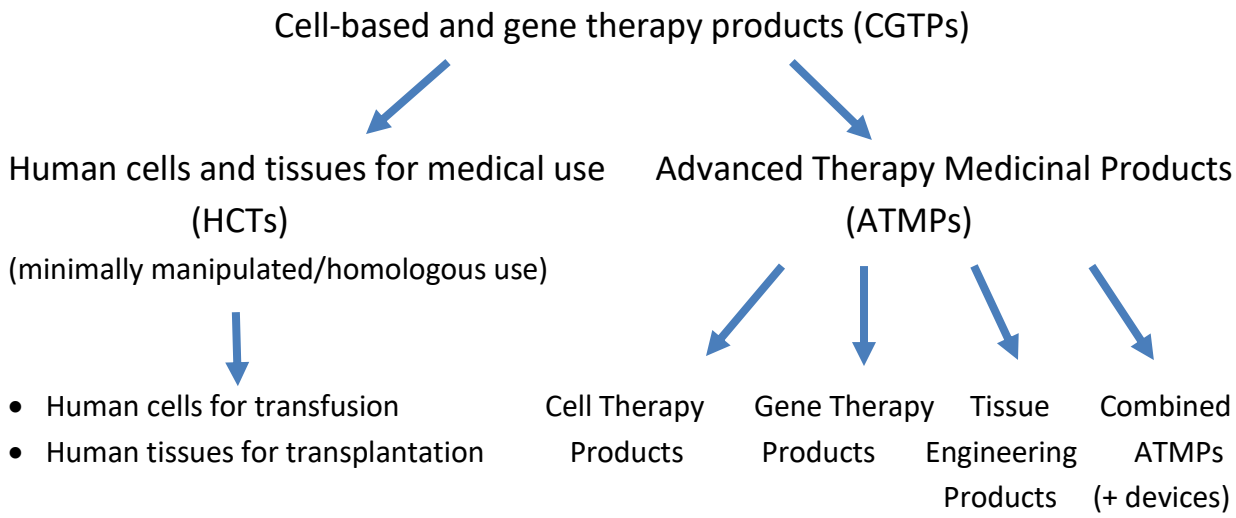
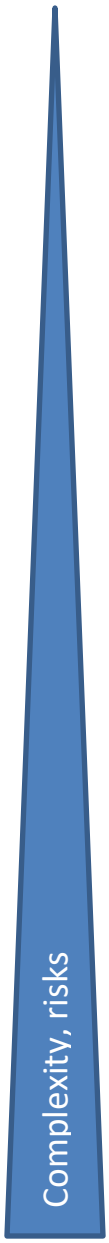


Figure 1. CGTPs can be subcategorized according to the risk associated with their use. Cells and tissues in HCTs are mainly of human origin, whereas those in ATMPs may be of human or animal (xenogeneic) origin (see clarifications of the definitions of different ATMP classes in the glossary).

In contrast to HCTs that are minimally manipulated and undergo homologous use, ATMPs are more complex because they require controlled steps for manufacturing and significant manipulation of the cellular or genetic starting material for the intended effect. In addition, their safety and efficacy cannot be predicted without well-controlled studies because living systems are highly complex, and their structure and/or function may be changed due to the manipulations and the production process. Therefore, ATMPs require more comprehensive regulation and demonstration of safety and efficacy, for which good quality, biological activity (32) and manufacturing consistency are proven for the products prior to marketing authorization (see currently available guidance for ATMPs in Appendix). ATMPs based upon replicating viral vectors, such as oncolytic viruses and other gene therapies using vectors that can replicate, require additional considerations and may present additional challenges since there is the potential for release into the environment and induction of viral disease or transmission to third parties. Products consisting of or containing replicating viral vectors require an environmental assessment to evaluate the potential adverse effects that could occur if the viral vector is released into the environment. Strategies need to be in place to mitigate such occurrence.

298 Table 1. Examples of CGTPs demonstrating broad range of product complexity and risks



Product class	Product type	Processing	Indication	Specific Risks
HCT	Autologous bone marrow cells	Collection of the bone marrow	Hematopoietic reconstitution	Minor
HCT	Allogeneic amniotic membrane	Collection and freeze drying, sizing	Treatment of ocular wounds	Minor
HCT	Allogeneic virus-specific T-cells	Collection, selection, washing and freezing of selected T-cells (no culture/expansion)	Treatment of severe infections	Disease transmission
ATMP / CTP[5]	Autologous PBMCs[1]	Collection, isolation and expansion of the cells, washing and formulation	Treatment of cardiac infarction	Disease transmission
ATMP / CTP	Allogeneic pluripotent stem cells (iPSC[2] / hESC[3])	Collection, purification, expansion, differentiation, formulation	Treatment of Retinitis Pigmentosa	Immuno-toxicity, tu-morigenicity
ATMP / GTP[6] *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 safety, immuno-toxicity
ATMP / GTP *ex vivo*	Lentivirus + globin gene in autologous CD34+ cells	LVV production using plasmids, purification and transduction into patient CD34+ cells, cell expansion and formulation	Treatment of β-thalassemia	Integrational mutagenesis, oncogenesis, viral safety
ATMP / GTP *ex vivo*	Allogeneic CD19 CAR[4] T-cells	Construction of the CAR into LVV, removal of HLA[7]-genes from the T-cells with gene editing, expansion, formulation	Hematopoietic malignancies, off-the-shelf	Genotoxicity, Immuno-toxicity, Integrational mutagenesis, neurotoxicity

299 [1] PBMCs= Peripheral Mononuclear Cells
300 [2] iPSC = Induced Pluripotent Stem Cells
301 [3] hESC = Human Embryonic Stem Cells
302 [4] CAR = Chimeric Antigen Receptor
303 [5] CTP= Cell Therapy Product
304 [6] GTP = Gene Therapy Product
305 [7] HLA = Human Leukocyte Antigen

The wide range of products that constitute ATMPs creates significant challenges in their regulation as a class overall. As for other CGTPs, controlled manufacturing of ATMPs requires a consistent process that assures such elements as identity, purity and biological activity, and freedom from adventitious agents including viruses, bacteria, and fungi. An important aspect of development of ATMPs is the identification and determination of critical quality attributes for each product. Critical quality attributes consist of physical, chemical, biological, or microbiological properties or characteristic(s) of a product that should be within an appropriate limit, range, or distribution to ensure the desired target product quality. Ideally, a critical quality attribute would correlate with clinical effectiveness also. An example of a critical quality attribute 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.

Long-term safety and efficacy follow-up of individuals treated with ATMPs can present unique challenges because unlike conventional drugs and biologics, these products may exert their effects for years following administration. For example, Lentivirus vector transduced CD34+ cells that are systemically administered to correct a genetic defect could exert its effect for years through its integrated presence in cells. Thus, the risk of insertional mutagenesis should be addressed in pre-clinical and clinical studies and the availability of 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 *(33)*. The duration of such safety surveillance needs to be carefully considered to ensure optimal collection of events, yet not unduly burdensome for the patients who receive the gene therapy product.

Common Regulatory Expectations

Working towards global convergence on regulatory expectations for CGTPs, and ultimately regulatory harmonization, will benefit patients in all regions of the world by helping to facilitate access to these potentially transformative products, which are among the most advanced medical products available. Harmonization is the key to support 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 harmonization, CGTPs can be divided into two categories: (1) ATMP products that require pre-market authorization, and; (2) HCT products that do not have this requirement as they fall in the lower risk category. The criteria required to make this determination include addressing some fundamental questions: 1) is the product a gene therapy? 2) does the product contain viable nucleated cells? 3) is the product intended for homologous use? and 4) is the product minimally manipulated? HCT products that do not require authorization can generally be regulated with less stringent measures to prevent the transmission of infectious diseases. However, ATMPs across a spectrum of complexity and risks

(see Table 1.), require more stringent regulation. A schematic overview of the considerations for determining risk level is shown in Figure 2.

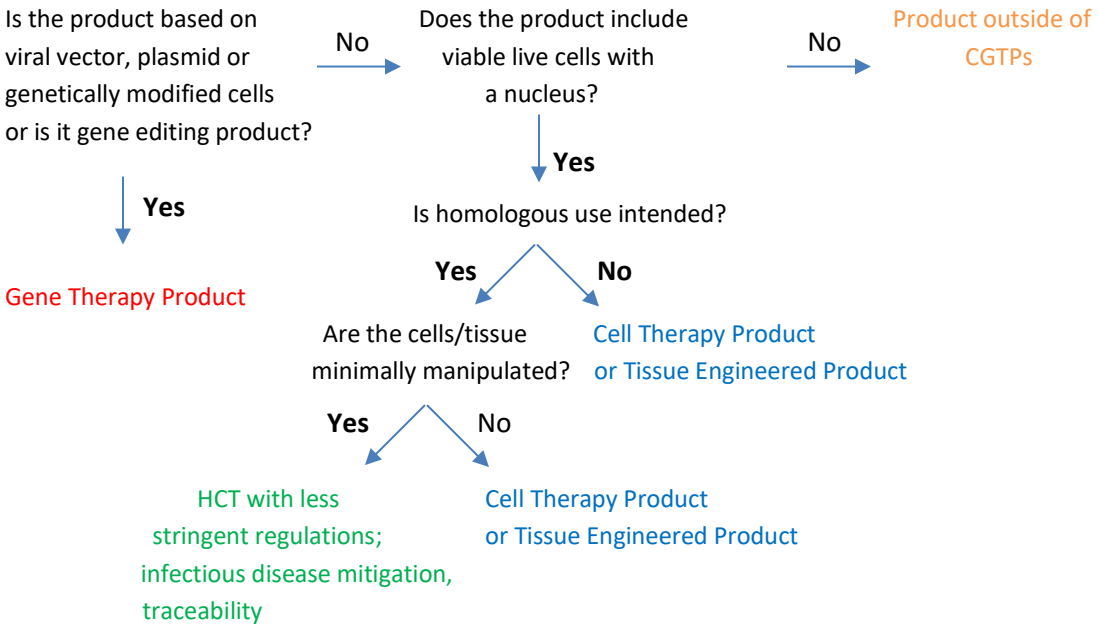


Figure 2. A proposed schema for the regulatory path based on classification of the CGTPs. The definitions of minimal manipulation and homologous use are provided in the glossary.

Application of a Risk-Based Approach

Although CGTPs have the potential to bring tremendous benefit to individuals in medical need, they also have the potential to cause serious harm if not used properly. There needs to be careful consideration of each product and its development and deployment under appropriate regulatory oversight. The maturity of regulatory systems for oversight of CGTPs varies widely among high-, middle-, and low-income countries. It is critical for all regulatory authorities responsible for oversight of medicinal products to be familiar with the potential risks and regulatory considerations for CGTPs. Conduct of investigational studies or deployment of these products, especially ATMPs, without regulatory oversight and adequate safety monitoring can result in severe adverse outcomes for the treated patients. It is critical to understand the nature of the products and the appropriate level of regulation required for different categories of CGTPs to prevent unscrupulous developers from taking advantage of vulnerable patients and less advanced regulatory environments.

A risk-based approach could be a feasible way to regulate CGTPs, depending on maturity level of the regulatory authority and its expertise and available resources. 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 product. Since many CGTPs are derived or prepared from living organisms or are themselves living organisms, the prevention of infectious disease transmission is a fundamental aspect of regulatory oversight of these products. Particularly for the use of cells and tissues for transplantation from one individual to another, although premarket authorization is often felt to be unnecessary, it is critical that proper measures are in place to screen the donors of cells and tissues (either living or deceased/cadaveric) with a questionnaire or comparable assessment process for potential infectious diseases, and 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 attestation 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 medicinal 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 precautions as HCTs to prevent the transmission of infectious diseases. In addition, ATMPs require oversight of other key regulatory issues including:

1. manufacturing and quality controls of the ATMPs, including process changes and comparability assessments, for clinical trials and commercial production under Good Manufacturing Practice (GMP)
2. non-clinical studies to generate pharmacodynamic (PD), pharmacokinetic (PK), biodistribution and safety data for the products to ensure the risks are known and mitigated before human exposure (Good Laboratory Practice, GLP, required for pivotal safety studies)
3. clinical studies with proper design and control to collect robust and reliable safety and efficacy data for the products and long-term follow-up of the patients (Good Clinical Practice, GCP, required for conduct of the studies)

These aspects require that the authorities must have capacity and expertise to evaluate and authorise clinical trial applications, marketing authorization applications and oversee post-

marketing surveillance to monitor long-term safety and efficacy of the authorised ATMPs. In addition, the GXP quality system requires capacity to perform necessary inspections (GMP, GLP, GCP).

The diversity of CGTPs has the advantage that it allows tailoring of the regulatory framework for those products that a country may deploy in that jurisdiction. Use of HCTs that do not require premarket authorization can potentially be implemented in settings with more rudimentary regulatory systems as long as the appropriate regulatory framework is in place to ensure that transmission of infectious diseases is minimized, and that products can be traced and recalled if necessary. Under those circumstances, countries can potentially deploy HCTs even in situations where they are relatively resource constrained.

For oversight of ATMPs requiring clinical trials and authorization because of their risks, manufacturing complexity and intended use, several options exist. For jurisdictions that have already some experience with cell therapy and tissue engineering products and have an adequate safety surveillance system in place, it may be easier to proceed to review and approve less complex gene therapy products that do not have severe risks. For jurisdictions with more extensive experience with the approval of simple ATMPs that have established safety surveillance systems, it may be reasonable not only to review and approve marketing applications for those ATMPs, but also to allow the investigational use of these products locally under appropriate regulatory framework and ethics committee oversight. For jurisdictions with minimal experience with ATMPs and rudimentary or less well-developed safety surveillance systems, it could be possible to have cell therapy or tissue engineering products marketed following a review process that leads to local approval based on sufficient data. There are intermediate states between these various options that a jurisdiction could consider.

To increase access to quality-assured, safe and effective ATMPs, it is encouraged to promote collaboration between regulators regionally and globally and leverage resources more efficiently. Collaboration among regulators currently takes place through regulatory networks that promote cooperation for carrying out various regulatory processes for medical products. 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 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 *(36)*. For exchanges and sharing pharmacovigilance data, WHO member states benefit from the safety information of medical products from the WHO database. PIC/S increases mutual confidence in GMP inspections among member countries. Collaboration among regulators and convergence of regulatory requirements in different jurisdictions increases efficiencies and promotes opportunities for reliance. Such regulatory reliance is needed even more for ATMPs than for traditional medical

products, given the lack of experience of regulators in many countries with authorization of these products

Through various initiatives for regulatory reliance regionally and internationally, it is hoped that regulatory convergence will ultimately lead to regulatory harmonization. As jurisdictions deploy HCTs and ATMPs, dialogue between regulators will need to continue to take place on an ongoing basis facilitated by WHO and through venues such as Asian-Pacific Economic Co-operation (APEC) *(37)*, International Pharmaceutical Regulators Programme (IPRP) *(38)* and others, with the goal of further regulatory convergence and harmonization. Global alignment on regulatory requirements for HCTs and ATMPs would benefit public health by making potentially transformative, safe and efficacious medical products available to more patients around the world.

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 to 26 October, 2018). Available from https://iris.paho.org/bitstream/handle/10665.2/51558/pahohss19004_eng.pdf?sequence=1&isAllowed=y

2. FDA Guidance for Industry HCT- and CTB products, minimal manipulation and homologous use. Available from https://www.fda.gov/media/109176/download

3. Regulation (EC) No. 1394/2007 of the European Parliament and of the Council on Advanced Therapy Medicinal Products and amending Directive 2001/83/EC and Regulation (EC) No. 726/2004. OJ L 2007;324:121–137. Available from https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-1/reg_2007_1394/reg_2007_1394_en.pdf

4. Alliance for Regenerative Medicine Annual Report 2020. Available from https://alliancerm.org/sector-report/2020-annual-report/

5. Rao M, Mason C, Solomon S. Cell therapy worldwide: an incipient revolution. Regen Med. 2015; 10(2):181-91.

6. High KA, Roncarolo MG. Gene Therapy. N Engl J Med. 2019;381(5):455-464. doi: 10.1056/NEJMra1706910.

7. Cicalese MP, Aiuti A. New perspectives in gene therapy for inherited disorders. Pediatr Allergy Immunol. 2020;31 Suppl 24:5-7. doi: 10.1111/pai.13149.

8. Rousseau, C.F., Mačiulaitis, R., Śladowski, D., and Narayanan, G. Cell and Gene Therapies: European View on Challenges in Translation and How to Address Them Front. Med 2018; 5:158. doi: 10.3389/fmed.2018.00158

9. U.S. FDA: Preclinical Assessment of Investigational Cellular and Gene Therapy Products (2013), available from https://www.fda.gov/media/87564/download

10. Salmikangas P, Menezes-Ferreira M, Reischl I, et al. Manufacturing, characterization and control of cell-based medicinal products: challenging paradigms toward commercial use. Regen Med. 2015;10(1):65-78. doi: 10.2217/rme.14.65.

11. Roddie C, O'Reilly M, Dias Alves Pinto J, Vispute K, Lowdell M. Manufacturing chimeric antigen receptor T cells: issues and challenges. Cytotherapy. 2019; 21(3):327-340. doi: 10.1016/j.jcyt.2018.11.009

12. Goula A, Gkioka V, Michalopoulos E, Katsimpoulas M, Noutsias M, Sarri EF, Stavropoulos C, Kostakis A. Advanced Therapy Medicinal Products Challenges and Perspectives in Regenerative Medicine. J Clin Med Res. 2020; 12(12):780-786. doi: 10.14740/jocmr3964.

13. U.S. FDA: Long Term Follow-Up After Administration of Human Gene Therapy Products. Available from https://www.fda.gov/media/113768/download

14. Directive 2004/23/EC of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells (2004). Off J L102:48-58

15. Directive 2009/120/EC 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. Available from https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-1/dir_2009_120/dir_2009_120_en.pdf

16. Bailey AM, Arcidiacono J, Benton KA, Taraporewala Z, Winitsky S. United States Food and Drug Administration Regulation of Gene and Cell Therapies. Adv Exp Med Biol. 2015;871:1-29. doi: 10.1007/978-3-319-18618-4_1. PMID: 26374210.

17. Maeda, D., Yamaguchi, T., Ishizuka, T., Hirata, M., Takekita, K. and Sato, D. Regulatory frameworks for Gene and Cell Therapies in Japan. Regulatory Aspects of Gene Therapy and Cell Therapy Products (2015); 147-163

18. Ridgway, A., Agbanyo, F., Wang, J. and Rosu-Myles, M. Regulatory Oversight of Cell and Gene Therapy Products in Canada. Adv Exp Med Biol.2015; 871:49-71. doi: 10.1007/978-3-319-18618-4_3.

19. NHS: Regenerative Medicine in the UK (2018), available from https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/regenerative-medicine/

20. Choi, M., Han, E., Lee, S., Kim, T. and Shin, W. Regulatory Oversight of Gene Therapy and Cell Therapy Products in Korea. Regulatory Aspects of Gene Therapy and Cell Therapy Products (2015); 163-179.

21. Health Sciences Authority, Singapore: Regulatory overview of cell, tissue or gene therapy products, available from https://www.hsa.gov.sg/ctgtp/regulatory-overview

22. Lin YC, Wang PY, Tsai SC, Lin CL, Tai HY, Lo CF, Wu SI, Chiang YM, Liu LL. Regulation of Cell and Gene Therapy Medicinal Products in Taiwan. Adv Exp Med Biol. 2015; 871:181-94. doi: 10.1007/978-3-319-18618-4_10. PMID: 26374219.

23. Volarevic V, Markovic BS, Gazdic M, Volarevic A, Jovicic N, Arsenijevic N, Armstrong L, Djonov V,

564 Lako M, Stojkovic M. Ethical and Safety Issues of Stem Cell-Based Therapy. Int J Med Sci. 2018;
565 15(1):36-45. doi: 10.7150/ijms.21666. eCollection 2018.

566 24. Anguela XM, High KA. Entering the Modern Era of Gene Therapy. Annu Rev Med. 2019; 70:273-
567 288. doi: 10.1146/annurev-med-012017-043332

568 25. 2018 International Conference of Drug Regulatory Authorities (ICDRA) meeting report, WHO Drug
569 Information Vol. 31, No. 4, Page 517, 2018; available at
570 https://www.who.int/medicines/areas/quality_safety/regulation_legislation/icdra/
571 WHO_DI_32-4_18ICDRA.pdf
572
573 26. Schneider CK, Salmikangas P, Jilma B, Flamion B, et al. Challenges with advanced therapy medicinal
574 products and how to meet them. Nat Rev Drug Discov. 2010;9(3):195-201. doi: 10.1038/nrd3052.

575 27. Srivastava A, Mason C, Wagena E, Cuende N, Weiss DJ, Horwitz EM, Dominici M. Part 1: Defining
576 unproven cellular therapies. Cytotherapy. 2016;18(1):117-9. doi: 10.1016/j.jcyt.2015.11.004.
577 PMID: 26719202.

578 28. WHO Expert Committee on Biological Standardization: sixty-seventh report. Geneva: World Health
579 Organization, Page 36 - 38, 2016 (WHO Technical Report Series, No. 1004;
580 https://www.who.int/publications/i/item/9789241210133)

581 29. Hayakawa T, Aoi T, Bravery C, Hoogendoorn K, Knezevic I, Koga J et al. (2015). Report of the
582 international conference on regulatory endeavors towards the sound development of human cell
583 therapy products. Biologicals; 43 (5) 283-297. doi: 10.1016/j.biologicals.2015.07.009. Epub 2015
584 Aug 24.

585 30. Petricciani J, Hayakawa T, Stacey G, Trouvin JH, Knezevic I. (2017) Scientific considerations for the
586 regulatory evaluation of cell therapy products. Biologicals. 2017 Nov; 50:20-26.

587 31. Abbot S, Agbanyo F, Ahlfors JE, Baghbaderani BA, Bartido S, Bharti K et al. (2018) Report of the
588 international conference on manufacturing and testing of pluripotent stem cells. Biologicals. 2018
589 Nov; 56:67-83. doi: 10.1016/j.biologicals.2018.08.004. Epub 2018 Aug 24.

590 32. Bravery CA, Carmen J, Fong T, Oprea W, Hoogendoorn KH, Woda J, Burger SR, Rowley JA, Bonyhadi
591 ML, Van't Hof W. Potency assay development for cellular therapy products: an ISCT review of the
592 requirements and experiences in the industry. Cytotherapy. 2013 Jan;15(1):9-19. doi:
593 10.1016/j.jcyt.2012.10.008. PMID: 23260082.

594 33. Reflection paper on management of clinical risks deriving from insertional mutagenesis
595 (EMA/CAT/190186/2012), available from www.ema.europa.eu/en/documents/scientific-
596 guideline/reflection-paper-management-clinical-risks-deriving-insertional-mutagenesis_en.pdf
597
598 34. WHO / African Vaccine Regulatory Forum (AVAREF), available at African Vaccine Regulatory Forum

(AVAREF) | WHO | Regional Office for Africa

35. ASEAN Joint Assessment Procedure for Pharmaceutical Products, available at ASEAN Joint Assessment Procedure for Pharmaceutical Products (hsa.gov.sg)

36. Australia-Canada-Singapore-Switzerland-United Kingdom (Access) Consortium, available at https://www.tga.gov.au/australia-canada-singapore-switzerland-united-kingdom-access-consortium

37. Asia-Pacific Economic Co-operation (APEC), available at Asia-Pacific Economic Cooperation (apec.org)

38. International Pharmaceutical Regulators Programme (IPRP), available at IPRP – International Pharmaceutical Regulators Programme

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:

1. 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.

2. 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.

3. 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.

4. ISO, ISO 23033:2021; Biotechnology — Analytical methods — General requirements and considerations for the testing and characterization of cellular therapeutic products; https://www.iso.org/standard/74367.html; ISO/TS 23565:2021, Biotechnology — Bioprocessing — General requirements and considerations for equipment systems used in the manufacturing of cells for therapeutic use, https://www.iso.org/standard/76053.html

   ISO guides principles for testing and characterization of cell therapy products. These principles could be used to set up critical quality attributes of specific cell therapy products. They also provide minimum requirements for various types of equipment in the process of cells for manufacturing of cell therapy products.

5. 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

683 therapy products (CTP) was formally finalized and approved by the members of the INN Expert
684 Group designated to deal with the selection of international nonproprietary names. Mandatory
685 information for INN selection and publication for cell-based therapies including cell-based gene
686 therapy substances is available to the applicant for new INN request submissions.
687
688 6. WHO, Human genome editing: recommendations (2021):
689 https://www.who.int/publications/i/item/9789240030381; Human genome editing: a framework for
690 governance (2021), https://www.who.int/publications/i/item/9789240030060; Human genome
691 editing: position paper (2021), https://www.who.int/publications/i/item/9789240030404

692 WHO provides recommendations on the governance and oversight of human genome editing in nine
693 areas, including human genome editing registries. WHO also provides a new governance framework
694 that identifies specific tools, institutions and scenarios to illustrate practical challenges in
695 implementing, regulating and overseeing research into the human genome.
696
697 7. WHO, Principles on the donation and management of blood, blood components and other medical
698 products of human origin (2017):
699 https://apps.who.int/iris/bitstream/handle/10665/274793/A70_19-
700 en.pdf?sequence=1&isAllowed=y

701 WHO recommends ten principles for promoting ethical practices in the donation and management
702 of medical products of human origin, including voluntary consent of the donor, safety, quality and
703 efficacy of donation and provides key considerations for implementation.
704
705 8. NIBSC, WHO 1st Reference Reagent for Lentiviral Vector Integration Site Analysis
706 https://www.nibsc.org/documents/ifu/18-144.pdf; 1st WHO International Reference Reagent CD4 T-
707 cells (human), https://www.nibsc.org/documents/ifu/15-270.pdf

708 NIBSC distributes WHO international measurement standards for assuring the quality of biological
709 medicines. Two WHO international measurement standards are available for cell and gene therapy
710 products. WHO 1st Reference Reagent for Lentiviral Vector Integration Site Analysis is suitable as a
711 qualitative Reference Reagent for LV integration site analysis, with a confident detection of the ten
712 defined LV integration sites. 1st WHO International Reference Reagent CD4 T-cells (human) are
713 intended for use as a cellular control for CD4 T cell enumeration by flow cytometry.
714