Global Harmonisation activities for ATMP

Kowid Ho, Technical regulatory policy
Roche Basel

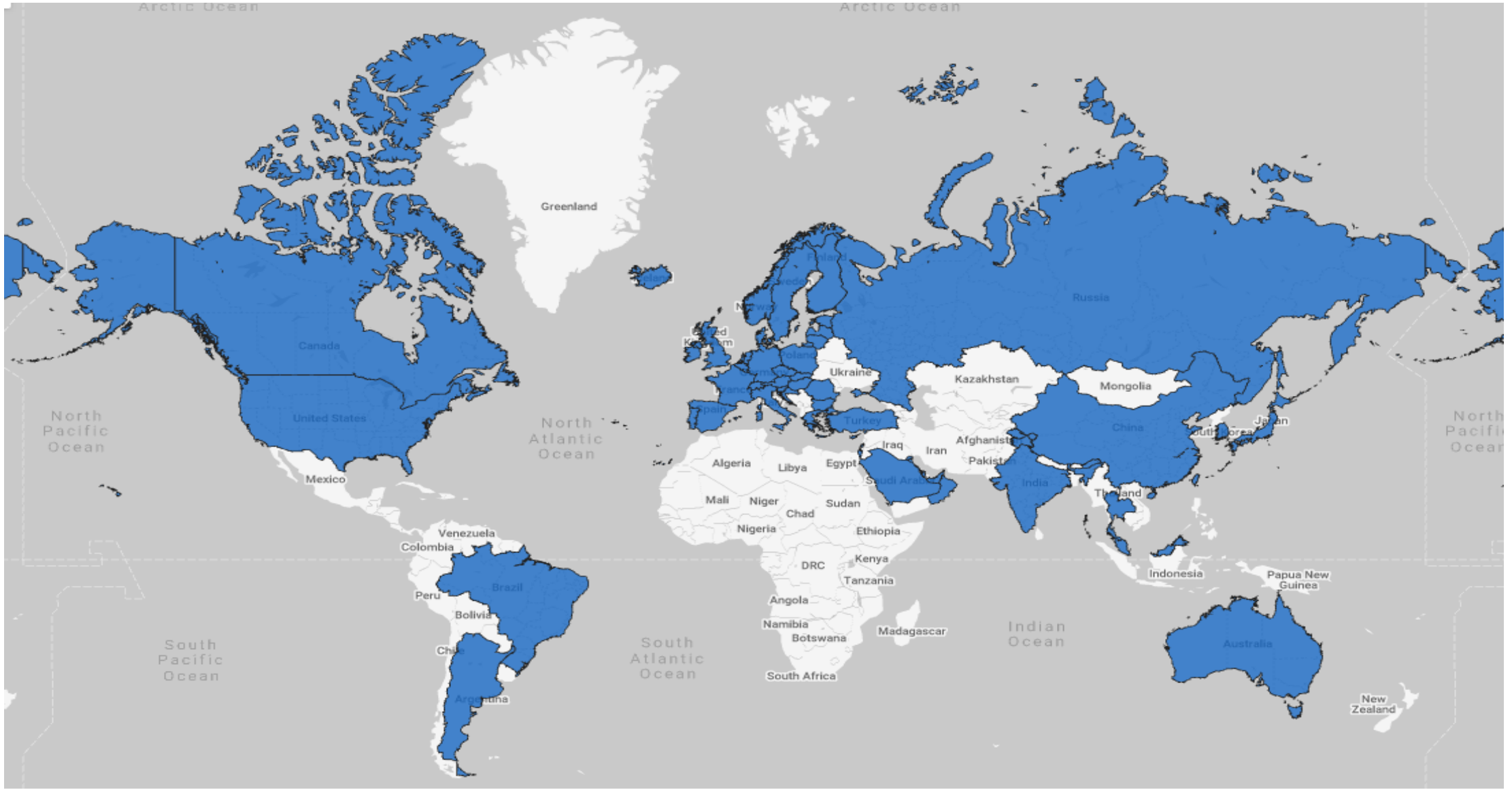
21 June 2024

Cell and gene therapy sector snapshot

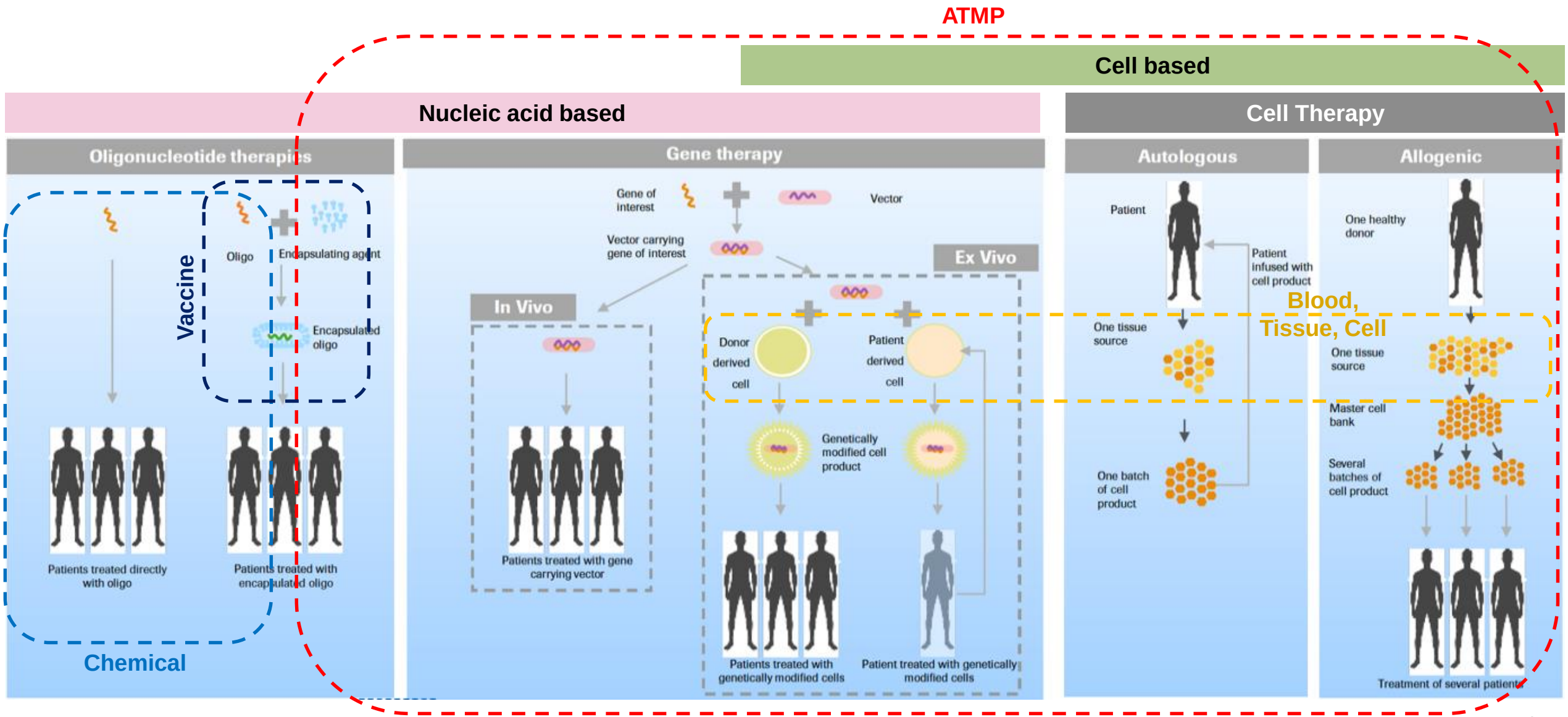
Roche

	North America	Asia Pacific	Europe	Total
Developers	1,235	888	543	2,760
Clinical Trials	917	648	329	1,687
Investment	$2.4B	$0.5B	$0.2B	$3.0B

Global CGT regulations - Guidelines/Regulations adopted or drafted

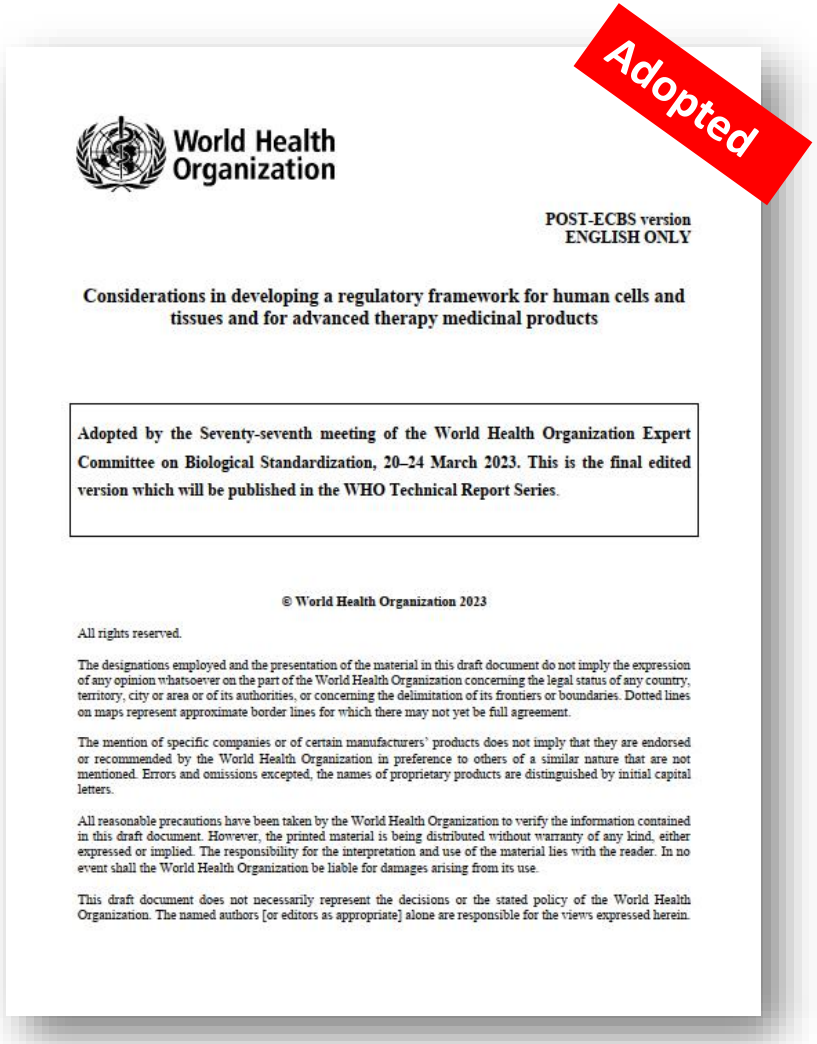


Different innovative modalities



World Health Organization

WHO consideration in developing a regulatory framework for human cells and tissues and for advanced therapy medicinal products - TRS 1048, Annex 3, 25 March 2023



Overview

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.

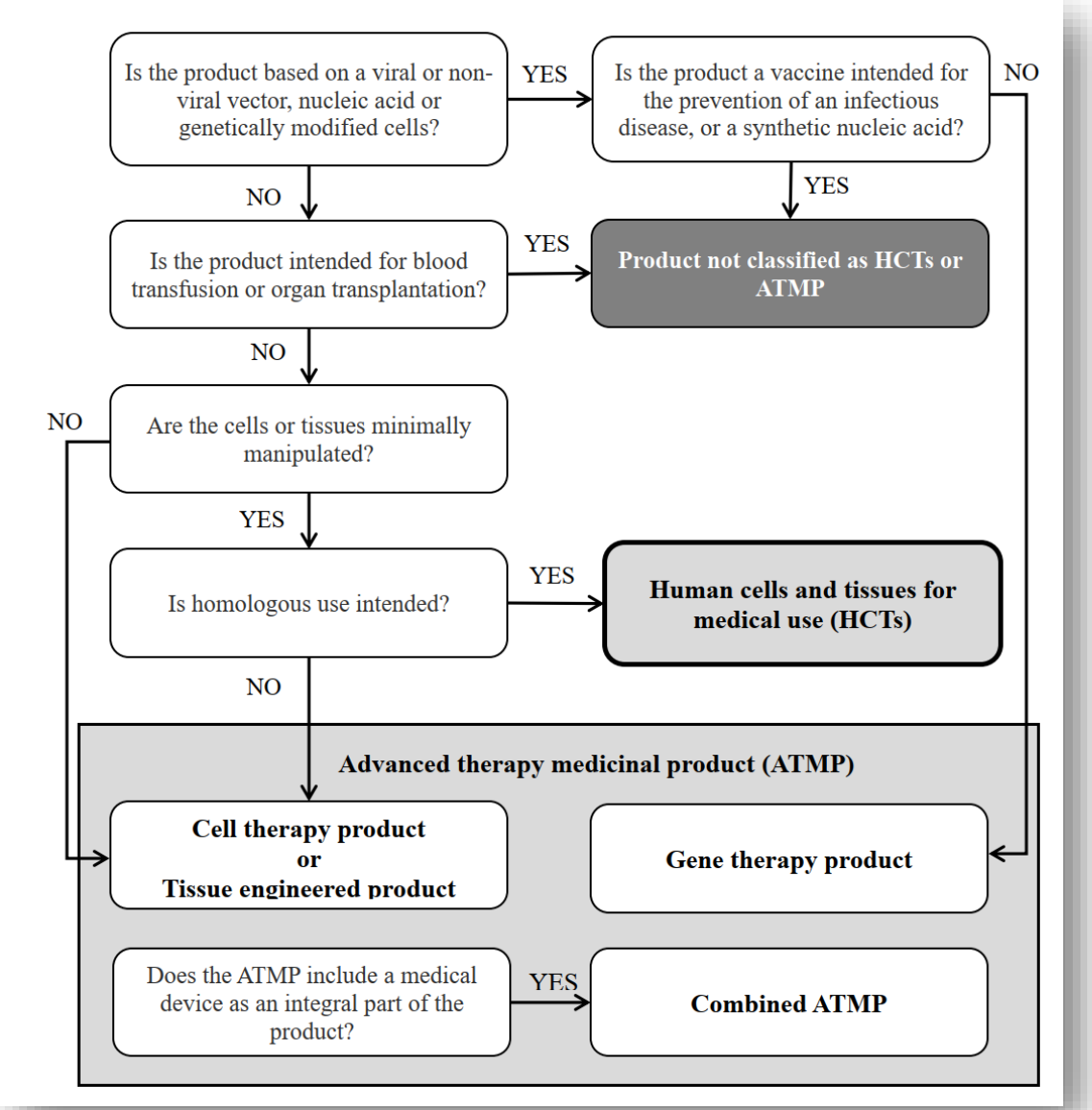
https://www.who.int/publications/m/item/considerations-in-developing-a-regulatory-framework-for-human-cells-and-tissues-and-for-advanced-therapy-medicinal-products

Annex 3

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

Purpose:

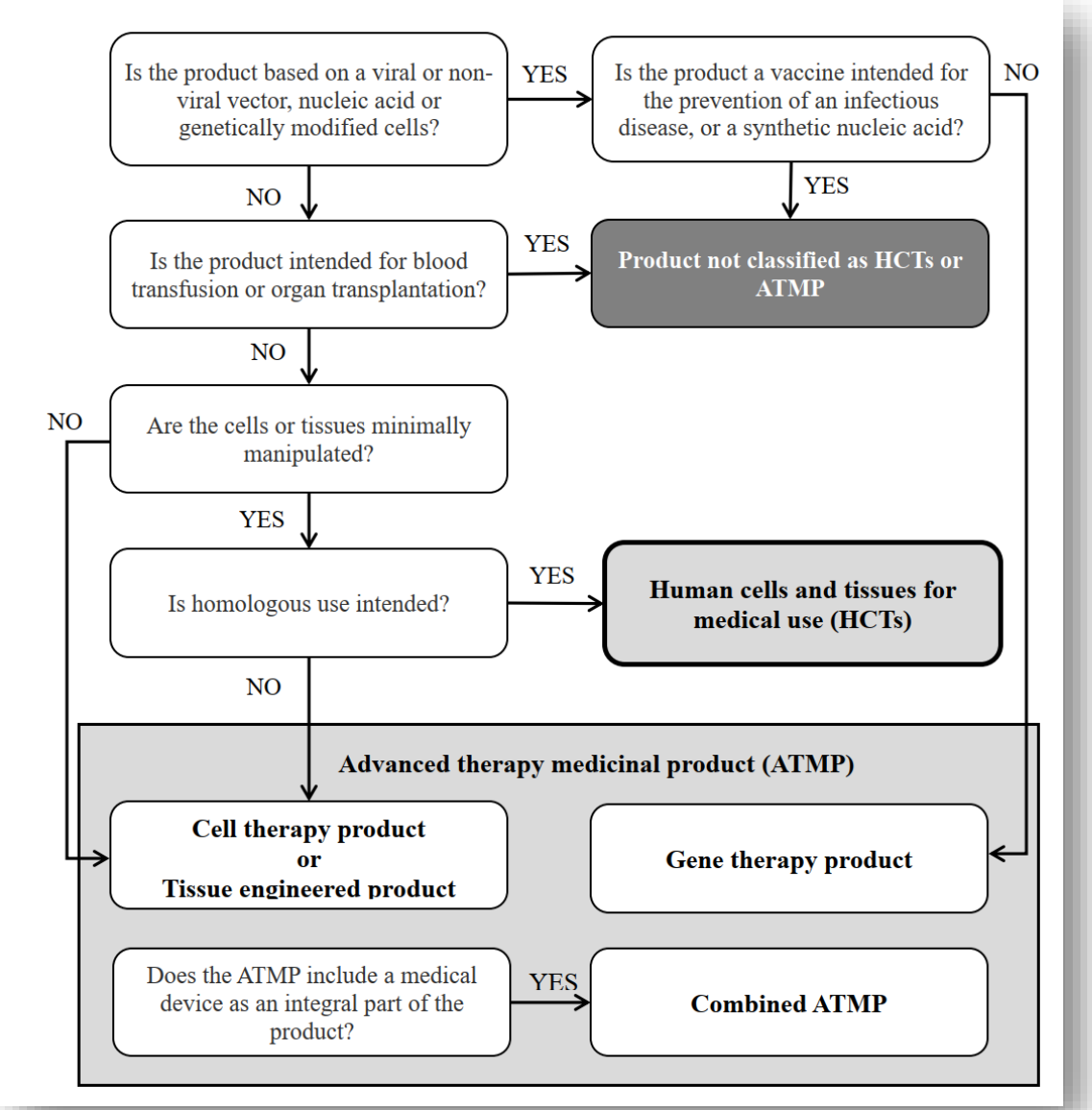
- Facilitate **global convergence among regulators from low-, middle- and high-income countries**
- Provide a set of basic **definitions and terminology** for this range of products
- Develop a common language and **risk-based classification** system
- Encourage the establishment of regulatory frameworks in countries where none exist
- **Encourage the use regulatory convergence and reliance** to build regulatory capacity and harmonization between countries and regions



- **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.
- **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.

https://www.who.int/publications/m/item/considerations-in-developing-a-regulatory-framework-for-human-cells-and-tissues-and-for-advanced-therapy-medicinal-products

World Health Organization



- **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.
- **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.

https://www.who.int/publications/m/item/considerations-in-developing-a-regulatory-framework-for-human-cells-and-tissues-and-for-advanced-therapy-medicinal-products

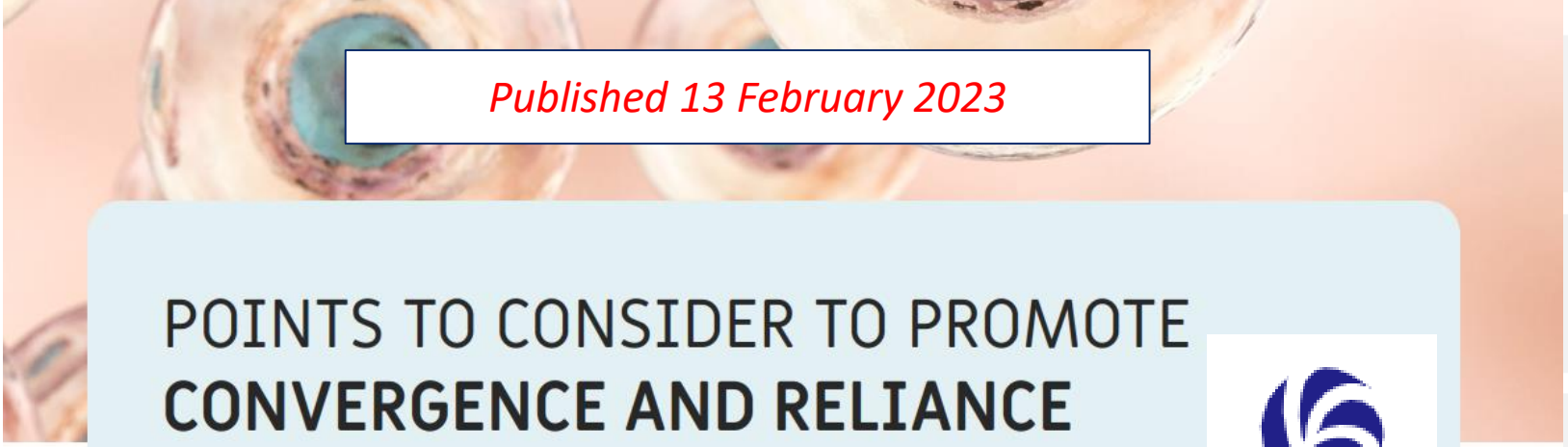
WHO Implementation Workshop on CGTPs

- Date/ Venue: 14 – 16 May 2024/ Muscat Oman
- 68 participants from 31 countries across 6 WHO regions;
  - Including 52 regulators/experts, 9 manufacturers from IFPMA, DCVMN and individual manufacturers, 7 WHO staff (HQ, EMRO, AFRO, WR Oman)
- Objectives:
  - Facilitate the implementation of WHO document on CGTPs into regulatory and manufacturing practices;
  - Provide the key principles in the WHO considerations;
  - Share regulatory/development experience and country situations;
  - Improve regulatory convergence in CGTPs

Regulatory status on CGTPs based on questions

	No regulatory pathway for CT and/or MA	Regulatory pathway for CT and/or MA	CGTP-specific regulation or guidelines
AFR	Nigeria, Zambia	Ghana, South Africa (CT), Tanzania	
AMR	Mexico		Argentina, Brazil, Canada, Chile, US
EMR	Tunisia	Egypt, Kuwait (MA), Morocco(CT), Pakistan	Jordan, Saudi Arabia
EUR			EU, Russia, UK
SEAR			India, Indonesia, Thailand
WPR			China, Japan, Korea, Singapore

* Questions on regulatory status were distributed to all participants from national regulatory authorities in advance (Feb. 2024)



Published 13 February 2023

POINTS TO CONSIDER TO PROMOTE CONVERGENCE AND RELIANCE APPROACHES FOR ATMP

IFPMA

EXECUTIVE SUMMARY

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

One of the challenges in regulating Cell, Tissue, and Gene therapies is to establish a clear definition that determines product classification for ATMPs and therefore the

applicability of the corresponding regulations. Considering the lower regulatory requirements applied to HCTs, it is of most importance that these definitions are clear and the corresponding classifications are transparent to regulatory authorities and sponsors.

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This paper discusses **the need to converge on the definitions and classification of ATMPs in order to foster reliance and/or recognition approaches to enable patients' access to ATMPs.**

Promote harmonization and recognition of product classification
RECOMMENDATIONS 1-2

Facilitate reliance, recognition and collaboration across ATMP lifecycle
RECOMMENDATIONS 3-6

Encourage harmonization of accreditation and standardization programs
RECOMMENDATIONS 7-8

Waive in-country testing
RECOMMENDATION 9

Use of "universal label" and electronic options
RECOMMENDATIONS 10-11

Recognize GMP compliant certification
RECOMMENDATION 12

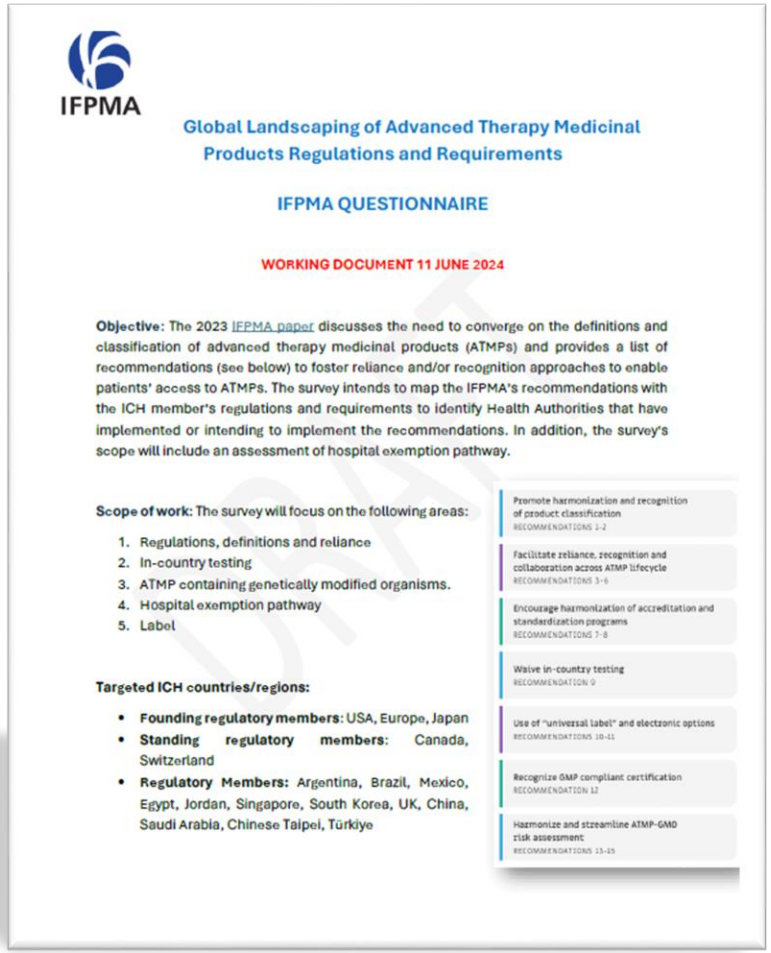
Harmonize and streamline ATMP-GMO risk assessment
RECOMMENDATIONS 13-15

https://www.ifpma.org/wp-content/uploads/2023/02/2022-position-paper-ATMP-convergence-and-reliance-ifpma-en.pdf

Activity in 2024: Framework mapping
Initial scope

- **Regulations, definitions and reliance**
- **In-country testing**
- **ATMP containing genetically modified organisms**
- **“Hospital exemption” pathway**
- **Label**

- **ICH regulatory members**
  - Founding regulatory members: USA, Europe, Japan
  - Standing regulatory members: Canada, Switzerland
  - Regulatory Members: Brazil, Mexico, Egypt, Singapore, South Korea, UK, China, Saudi Arabia, Chinese Taipei, Türkiye
  - New members (2024): Argentina, Jordan



IFPMA

Global Landscaping of Advanced Therapy Medicinal Products Regulations and Requirements

IFPMA QUESTIONNAIRE

WORKING DOCUMENT 11 JUNE 2024

Objective: The 2023 IFPMA paper discusses the need to converge on the definitions and classification of advanced therapy medicinal products (ATMPs) and provides a list of recommendations (see below) to foster reliance and/or recognition approaches to enable patients' access to ATMPs. The survey intends to map the IFPMA's recommendations with the ICH member's regulations and requirements to identify Health Authorities that have implemented or intending to implement the recommendations. In addition, the survey's scope will include an assessment of hospital exemption pathway.

Scope of work: The survey will focus on the following areas:

1. Regulations, definitions and reliance
2. In-country testing
3. ATMP containing genetically modified organisms.
4. Hospital exemption pathway
5. Label

Targeted ICH countries/regions:

- **Founding regulatory members:** USA, Europe, Japan
- **Standing regulatory members:** Canada, Switzerland
- **Regulatory Members:** Argentina, Brazil, Mexico, Egypt, Jordan, Singapore, South Korea, UK, China, Saudi Arabia, Chinese Taipei, Türkiye

Promote harmonization and recognition of product classification
RECOMMENDATIONS 1-2

Facilitate reliance, recognition and collaboration across ATMP lifecycle
RECOMMENDATIONS 3-6

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RECOMMENDATIONS 10-11

Recognize GMP compliant certification
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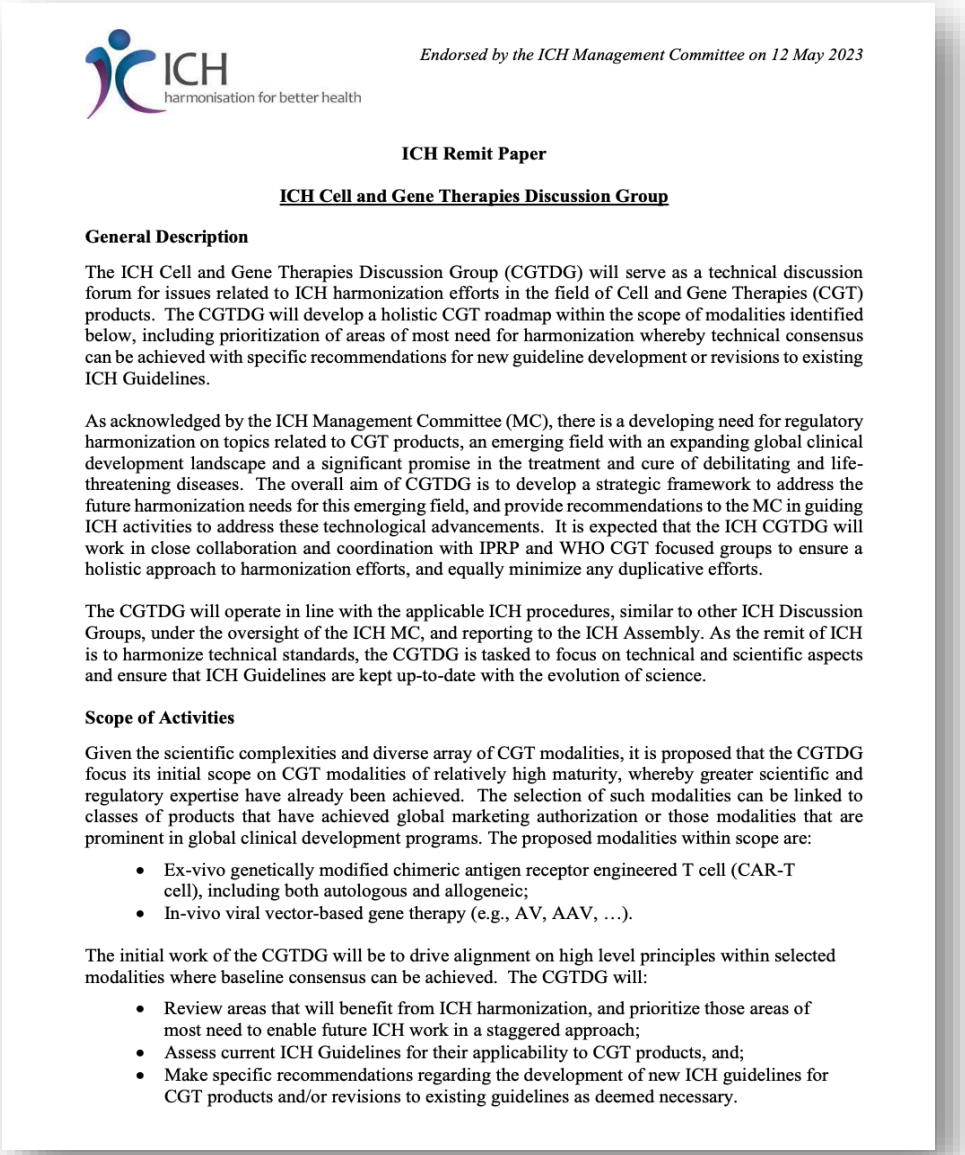
Harmonize and streamline ATMP-GMO risk assessment
RECOMMENDATIONS 13-15

ICH CGT DG Remit Paper

"The ICH Cell and Gene Therapies Discussion Group (CGTDG) will serve as a technical discussion forum for issues related to ICH harmonization efforts in the field of Cell and Gene Therapies (CGT) products. The CGTDG will develop a holistic CGT roadmap within the scope of modalities identified below, including prioritization of areas of most need for harmonization whereby technical consensus can be achieved with specific recommendations for new guideline development or revisions to existing ICH Guidelines."

Key Points:

- 2 Year Remit: covers clinical, CMC, and non-clinical
- AAVs & CAR-T (allo & auto) identified
  - "mature" modalities to be first in-scope
- The DG has been formed – Aug 2023



ICH harmonisation for better health

Endorsed by the ICH Management Committee on 12 May 2023

ICH Remit Paper

ICH Cell and Gene Therapies Discussion Group

General Description

The ICH Cell and Gene Therapies Discussion Group (CGTDG) will serve as a technical discussion forum for issues related to ICH harmonization efforts in the field of Cell and Gene Therapies (CGT) products. The CGTDG will develop a holistic CGT roadmap within the scope of modalities identified below, including prioritization of areas of most need for harmonization whereby technical consensus can be achieved with specific recommendations for new guideline development or revisions to existing ICH Guidelines.

As acknowledged by the ICH Management Committee (MC), there is a developing need for regulatory harmonization on topics related to CGT products, an emerging field with an expanding global clinical development landscape and a significant promise in the treatment and cure of debilitating and life-threatening diseases. The overall aim of CGTDG is to develop a strategic framework to address the future harmonization needs for this emerging field, and provide recommendations to the MC in guiding ICH activities to address these technological advancements. It is expected that the ICH CGTDG will work in close collaboration and coordination with IPRP and WHO CGT focused groups to ensure a holistic approach to harmonization efforts, and equally minimize any duplicative efforts.

The CGTDG will operate in line with the applicable ICH procedures, similar to other ICH Discussion Groups, under the oversight of the ICH MC, and reporting to the ICH Assembly. As the remit of ICH is to harmonize technical standards, the CGTDG is tasked to focus on technical and scientific aspects and ensure that ICH Guidelines are kept up-to-date with the evolution of science.

Scope of Activities

Given the scientific complexities and diverse array of CGT modalities, it is proposed that the CGTDG focus its initial scope on CGT modalities of relatively high maturity, whereby greater scientific and regulatory expertise have already been achieved. The selection of such modalities can be linked to classes of products that have achieved global marketing authorization or those modalities that are prominent in global clinical development programs. The proposed modalities within scope are:

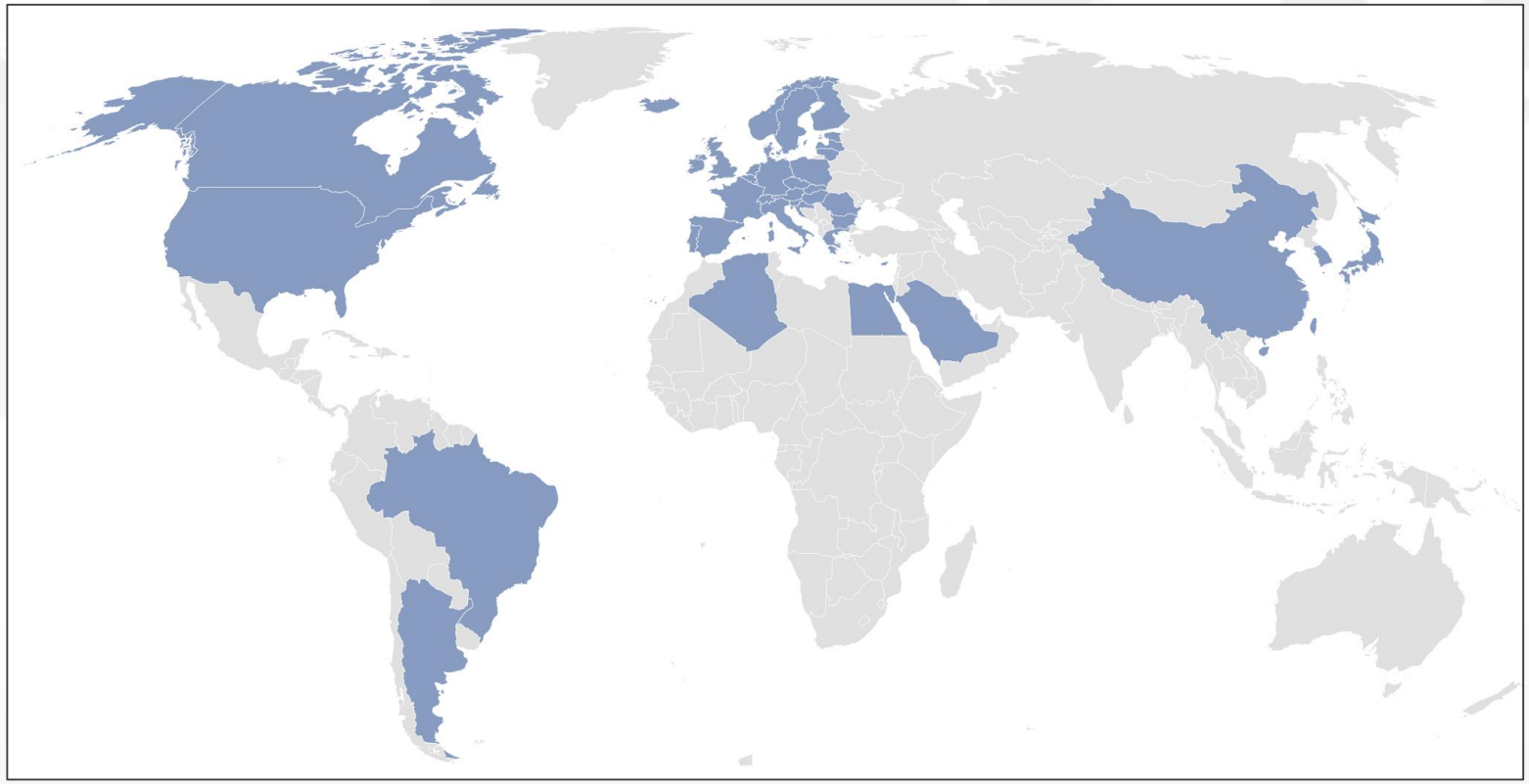
- Ex-vivo genetically modified chimeric antigen receptor engineered T cell (CAR-T cell), including both autologous and allogeneic;
- In-vivo viral vector-based gene therapy (e.g., AV, AAV, …).

The initial work of the CGTDG will be to drive alignment on high level principles within selected modalities where baseline consensus can be achieved. The CGTDG will:

- Review areas that will benefit from ICH harmonization, and prioritize those areas of most need to enable future ICH work in a staggered approach;
- Assess current ICH Guidelines for their applicability to CGT products, and;
- Make specific recommendations regarding the development of new ICH guidelines for CGT products and/or revisions to existing guidelines as deemed necessary.

https://admin.ich.org/sites/default/files/2023-07/ICH_CGTDG_Remit_2023_0512.pdf

ICH CGT DG Members



25 member organizations representing 45 countries

ICH CGT DG Members

Regulatory/Administrative Authorities

- EU commission, Europe
- FDA, USA
- MHLW/PMDA, Japan
- ANVISA, Brazil
- EDA, Egypt
- HSA, Singapore
- MFDS, Republic of Korea
- MHRA, UK
- NMPA, China
- SFDA, Saudi Arabia
- TFDA, Chinese Taipei
- Health Canada, Canada
- Swissmedic, Switzerland
- ANMAT, Argentina
- ANPP, Algeria

Industry Associations

- EFPIA
- JPMA
- PhRMA
- BIO
- IFPMA
- IGBA

Other/International Associations

- EDQM
- USP
- IPRP
- WHO

Rapporteur Supporter: Elaine Shults (BIO)

CGT DG to Advise Existing ICH WGs

- CGT DG is expected to provide expertise to existing ICH working groups (WGs) undergoing new guideline development or revisions where ATMPs are in scope.

- Completed: Review ATMP Annex for ICH Q1/Q5c Stability Revision EWG (January, 2024).

- CGT DG agreed to use the term Advanced Therapy Medicinal Product (ATMP).

Initial Scope of CGT DG

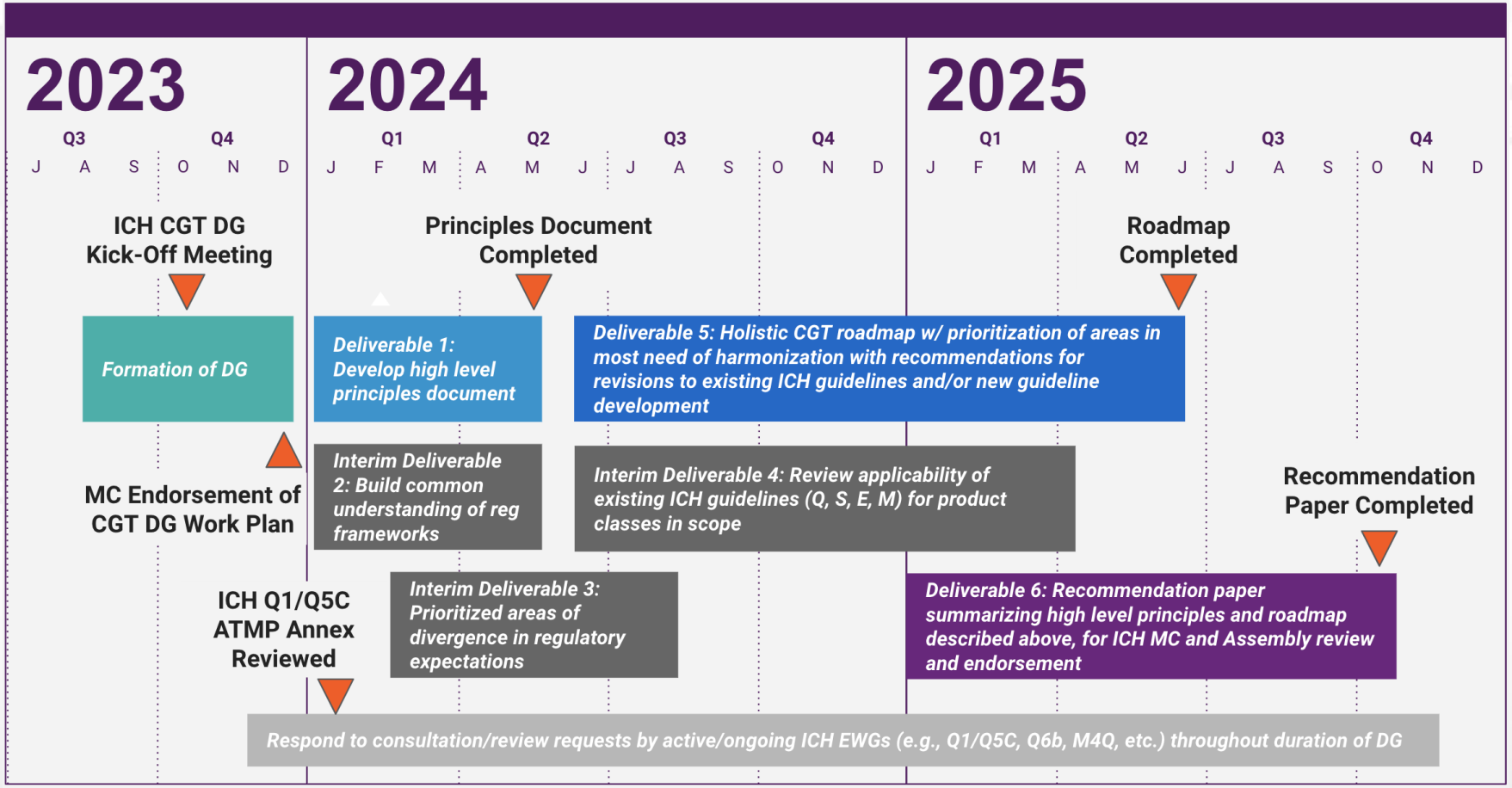
- Initial focus on CGT modalities of relatively high maturity.

- Classes of products with global marketing authorization or prominent in global clinical development programs.

  - *In vivo* viral vector-based gene therapy products (e.g. AAV vector-based gene therapies)

  - *Ex vivo* genetically modified cells (e.g. CAR T-cell products), both autologous and allogeneic

Work Plan Milestones Timeline



Deliverables Progressing in Parallel

- Work Plan reflects milestones outlined in remit paper.

- Deliverables:
  1. High level principles document
  2. Overview of global regulatory framework
  3. Areas of divergence and harmonization in regulatory expectations
  4. Stepwise review of existing ICH guidelines for applicability to ATMPs
  5. Holistic ATMP roadmap
  6. Recommendation paper

International Pharmaceutical Regulators Programme (IPRP)

- IPRP aims to create an environment for open discussion and sharing of best practices for the regulation of advanced therapies
- Support harmonization initiatives such as APEC and refer topics to appropriate organizations such as ICH, PIC/S, PANDRH, WHO
- Facilitate implementation of ICH and other internationally harmonised technical guidelines, promote collaboration and regulatory convergence
- Deliverables – postings on the IPRP website, publication of White Papers, journal manuscripts or ICH consideration papers
- Working groups:
  - Bioequivalence for generics
  - Biosimilars
  - **Cell and gene therapy**
  - Identification of medical products
  - Nanomedicines
  - Quality
  - Pharmacovigilance

https://www.iprp.global/working-groups

International Pharmaceutical Regulators Programme (IPRP)
Cell & Gene Therapy Working Groups

- Group of 18 regulators, and WHO and PAHO/PANDRH, discuss via quarterly teleconference
- At each meeting or teleconference, a roll call of regulatory updates to include new regulations, new guidance or guidelines, and recently approved products takes place. An annual compilation of updates will be prepared to keep participants up-to-date on current activities for each region
- Deliverables:
  - International regulatory frameworks for Cell and Gene Therapies
  - Expectation for biodistribution assessment for gene therapy products
  - IPRP reflection paper - topic endorsed by ICH Assembly in June 2019 - ICH S12 *(Step 5 implementation phase - Nonclinical biodistribution considerations for gene therapy products)*
  - General considerations for raw materials used in the manufacture of human cell and gene therapy products

International Pharmaceutical Regulators Programme (IPRP)

14 November 2022

List of IPRP Members and Observers participating in:

Cell Therapy (CTWG)

- ANVISA, Brazil
- COFEPRIS, Mexico
- CPED, Israel
- EC, Europe
- FDA, United States
- Health Canada, Canada
- HSA, Singapore
- ISPCH, Chile
- MFDS, Republic of Korea
- MHLW/PMDA, Japan
- MoH, Indonesia
- NPRA, Malaysia
- SAHPRA, South Africa
- SFDA, Saudi Arabia
- Swissmedic, Switzerland
- TFDA, Chinese Taipei
- TGA, Australia
- Thai FDA, Thailand
- TITCK, Turkey

04 October 2022

List of IPRP Members and Observers participating in:

Gene Therapy (GTWG)

- ANVISA, Brazil
- CPED, Israel
- EC, Europe
- FDA, United States
- Health Canada, Canada
- HSA, Singapore
- ISPCH, Chile
- MFDS, Republic of Korea
- MHLW/PMDA, Japan
- MoH, Indonesia
- NPRA, Malaysia
- PAHO/PANDRH
- SAHPRA, South Africa
- SFDA, Saudi Arabia
- Swissmedic, Switzerland
- TFDA, Chinese Taipei
- TGA, Australia
- Thai FDA, Thailand
- TITCK, Turkey
- WHO

Collaboration on **Gen**e **T**herapies Global (CoGenT Global) Pilot

- Initial participation by Standing Regulatory Members of ICH
- Partners may participate in internal regulatory meetings and meetings that include the sponsor
- Specific regulatory reviews are shared and discussed with partners
- All meetings conducted and information shared under strict confidentiality agreements
- Goal is to increase the efficiency of the regulatory process, reducing time and cost for agencies and sponsors

From Peter Marks, ARM Cell & Gene State of the Industry Briefing January 8, 2024

ACCESS ATMP Working Group

- The Access Consortium is a medium-sized coalition of regulatory authorities that work together to promote greater regulatory collaboration and alignment of regulatory requirements
- The consortium comprises the national regulatory authorities of **Australia, Canada, Singapore, Switzerland and the United Kingdom**

Advanced Therapy Medicinal Products Working Group

In 2023, the Access Consortium established a working group for advanced therapy medicinal products (ATMPs). ATMP is a term used in the legislative framework implemented by the European Union to regulate cell therapies, gene therapies and tissue engineering products.

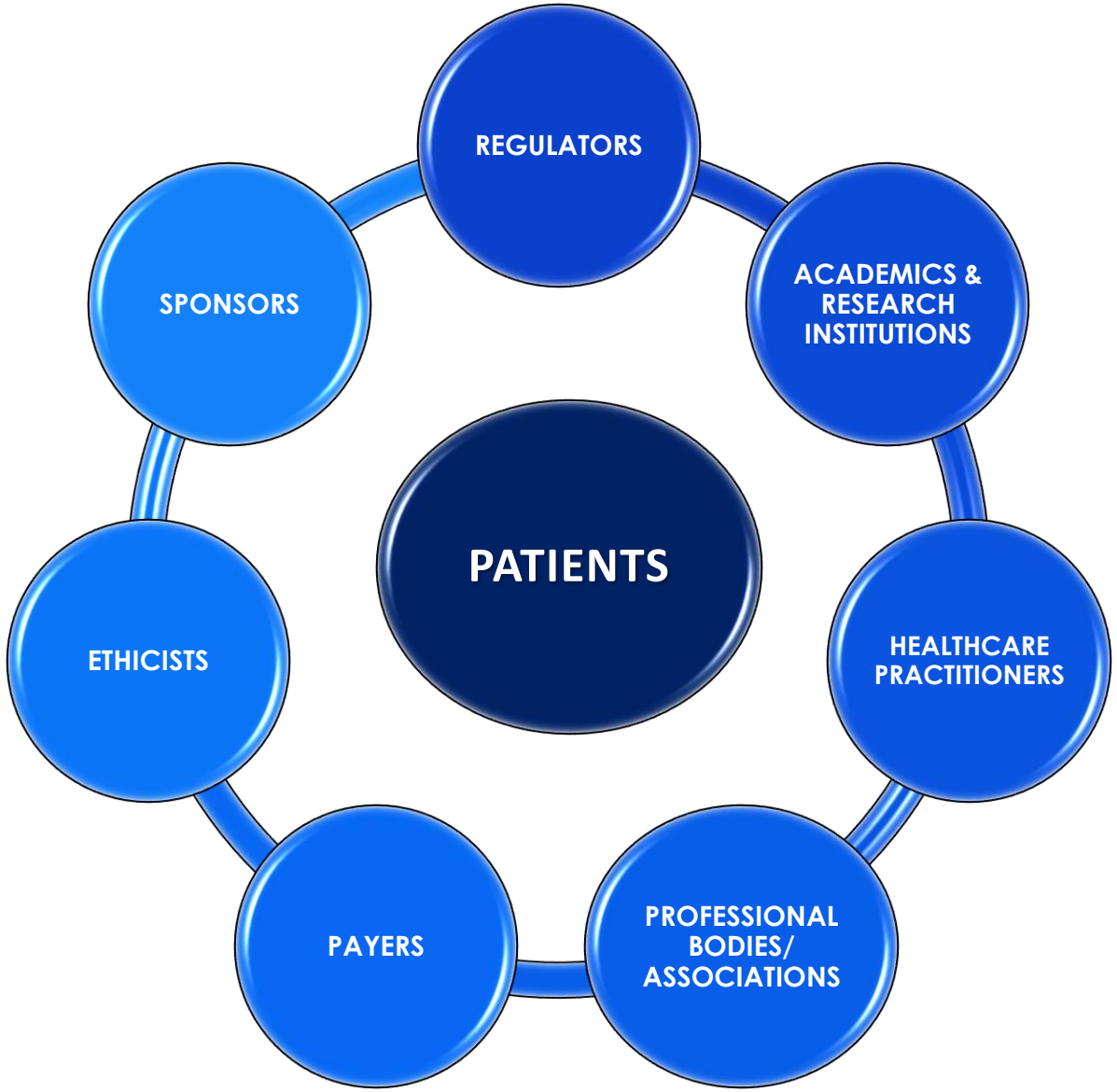
The main goals of this group are to:

- foster interdisciplinary (quality, non-clinical, clinical) scientific discussions on emerging innovative therapeutic concepts and technologies
- establish an interdisciplinary forum for Access members to discuss ATMP-specific topics with a focus on assessing benefits and risks and on regulatory decision-making
- encourage mutual exchange and harmonization on the regulatory assessment of ATMPs
- explore potential synergies and opportunities for work-sharing, reliance and providing joint scientific advice
- publish guidance and recommendations on common areas where the group has established a harmonized approach, where appropriate

https://www.tga.gov.au/international-activities/australia-canada-singapore-switzerland-united-kingdom-access-consortium

Conclusion

Multiparty engagement and collaboration

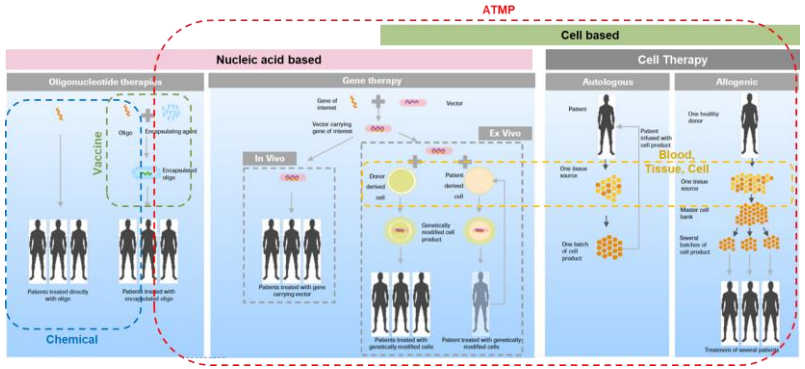


As newer therapies and technologies push the limits of regulatory and scientific expertise, manufacturers should proactively establish collaborations with other stakeholders throughout the product lifecycle, from early research to post-market activities, to bring novel and life-saving ATMPs to the market for the benefit of patients with unmet medical needs

Need for global collaboration

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

https://www.ifpma.org/publications/convergence-and-reliance-approaches-for-advanced-therapy-medicinal-products/m



Many different modalities; wide range of complexity

World Health Organization

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**

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RECOMMENDATIONS

IFPMA

3. Enable recognition and reliance approaches across the lifecycle of ATMPs. This should include products approved through expedited regulatory pathways.

4. NRAs are recommended to adopt a similar risk-based approach to data requirements consistent with the reference country filing package when implementing reliance.

5. Expand the scope of existing collaboration mechanisms for review of applications among several health authorities (e.g., marketing authorization, clinical trial, post marketing, scientific advice) to explicitly include ATMPs.

6. Promote participation in pilot programs for joint review and work-sharing (e.g., clinical trial, scientific advice) which allow expedited review pathways.

Doing now what patients need next