AN ANALYSIS OF THE ATMP REGULATORY LANDSCAPE IN ICH MEMBER COUNTRIES: OPPORTUNITIES AND CHALLENGES

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International Federation of Pharmaceutical Manufacturers and Associations,
Advanced Therapies Working Group

IFPMA

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AGENDA

- Introduction
- IFPMA:
  - 2023 recommendations
  - 2024-2025 mapping of recommendations with regulation in ICH member countries.
  - 2026 recommendations
- Conclusions & Outlook

INTRODUCTION

- ATMPs offer potential groundbreaking treatments for wide range of diseases and conditions where no currently effective therapeutic options.
- 50 FDA-approved cell and gene therapy products, and 34 ATMPs received positive opinions for marketing from the EMA (with 13 withdrawals).
- Global regulatory landscape for ATMPs is complex and varies significantly across countries and regions.
- Global demand for ATMPs is increasing, yet regulatory frameworks and requirements are not harmonized.
- Several countries actively working towards establishing specific regulations for ATMPs
    - Includes those that are members of The International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use (ICH).

IFPMA POSITION 2023 PAPER

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POINTS TO CONSIDER TO PROMOTE **CONVERGENCE AND RELIANCE APPROACHES FOR ATMP**

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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

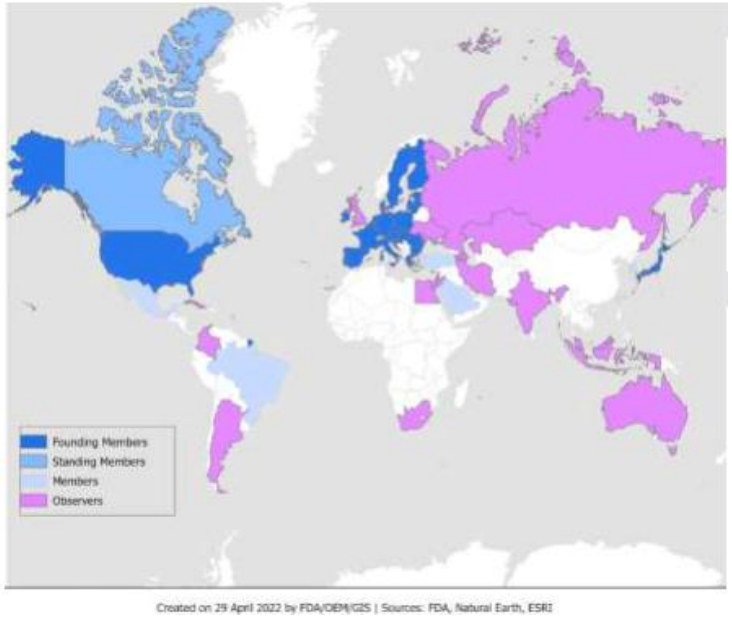
Waive in-country testing
RECOMMENDATION 9

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

Recognize GMP compliant certification
RECOMMENDATION 12

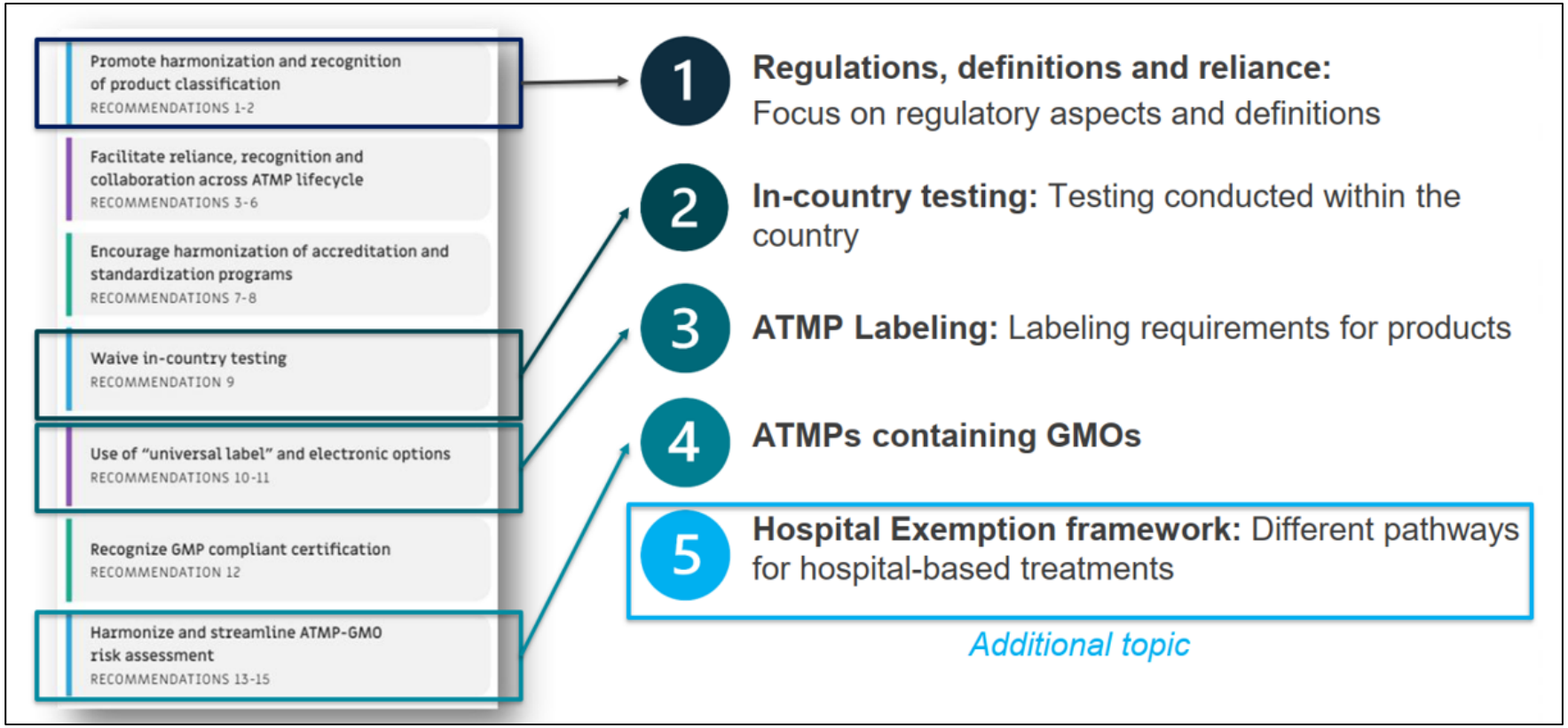
Harmonize and streamline ATMP-GMO risk assessment
RECOMMENDATIONS 13-15

IFPMA TOPICS MAPPED ACROSS 2024 ICH MEMBER COUNTRIES (17)



***Map* from 2022**

(Not taking into account 2025 updates, where Argentina now an ICH Member, and Peru and the Dominican Republic are Observers.)



Study encompassed ICH regulatory member countries, composed of founding regulatory members (Europe, Japan, USA), standing regulatory members (Canada, Switzerland) and regulatory members (Argentina, Brazil, China, Chinese Taipei, Egypt, Jordan, Republic of Korea, Mexico, Saudi Arabia, Singapore, Turkey, UK) **as of December 2024**.

METHODOLOGY

- Objective of analysis to map which National Regulatory Authorities already implemented, or plan to implement, IFPMAs recommendations.
- Survey questions developed for each topic based on the recommendations outlined by IFPMA in 2023.
- Data collected from agency websites, published literature by agency representatives, and from IFPMA member companies.
- Table summarises key questions per topic.

Area	Key themes of the survey questions
Regulatory landscape for ATMP therapies (regulations, definitions, reliance)	
Regulations, definitions	Does a country promote harmonization and recognition of product classification?
Reliance	Does a country facilitate reliance, recognition, and collaboration across ATMP lifecycle?
In-country testing	Does a country waive in-country testing?
ATMPs containing GMOs	Does a country harmonize and streamline ATMP-GMO risk assessment?
Labeling	Does a country use an 'universal label' and electronic options?
Hospital Exemption Framework	Has a country a framework for a Hospital Exemption?

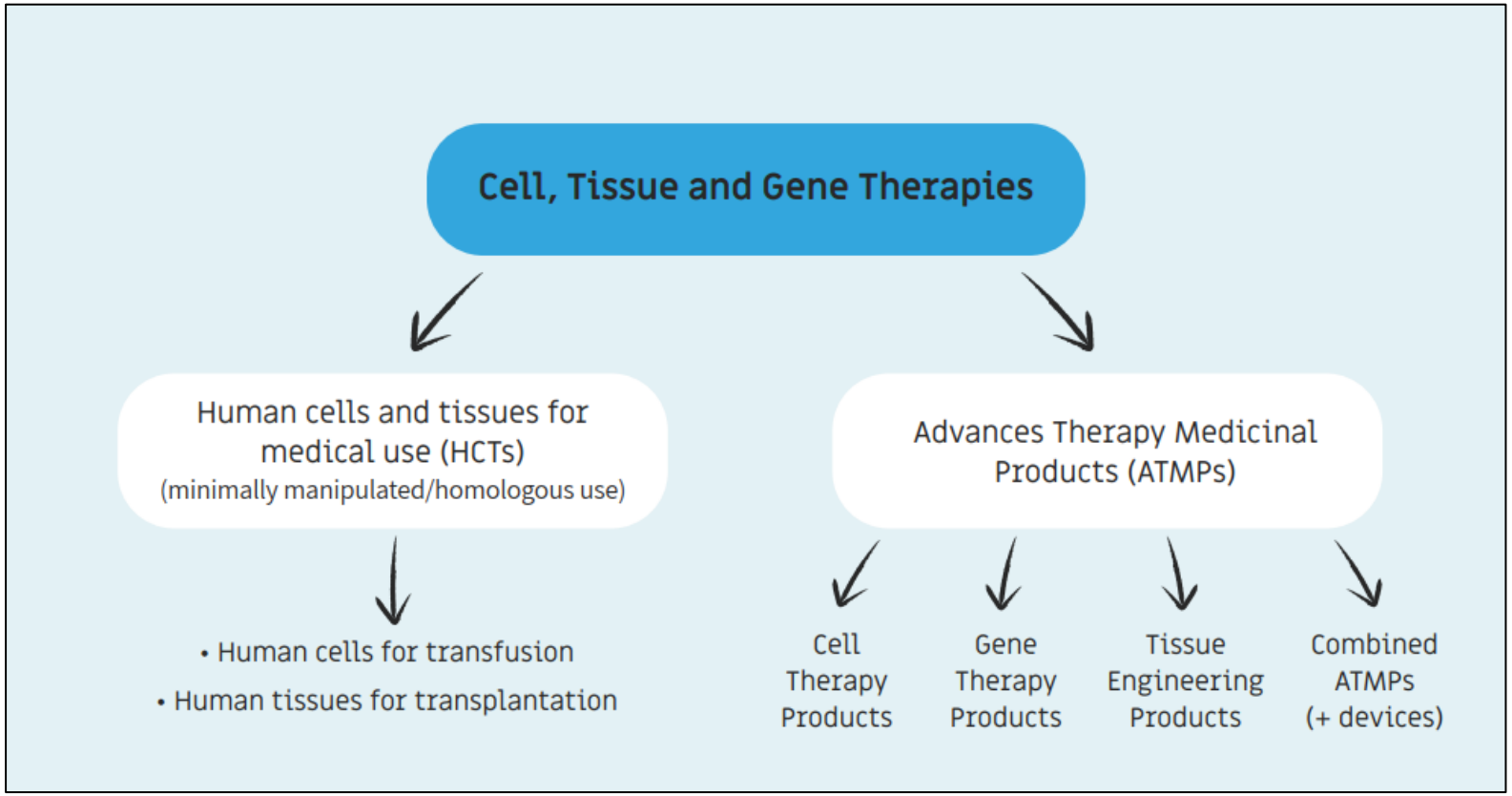
IFPMA POSITION 2023 PAPER RECOMMENDATIONS 1 & 2

LEGAL FRAMEWORK AND CLASSIFICATION OF ATMPS

RECOMMENDATIONS

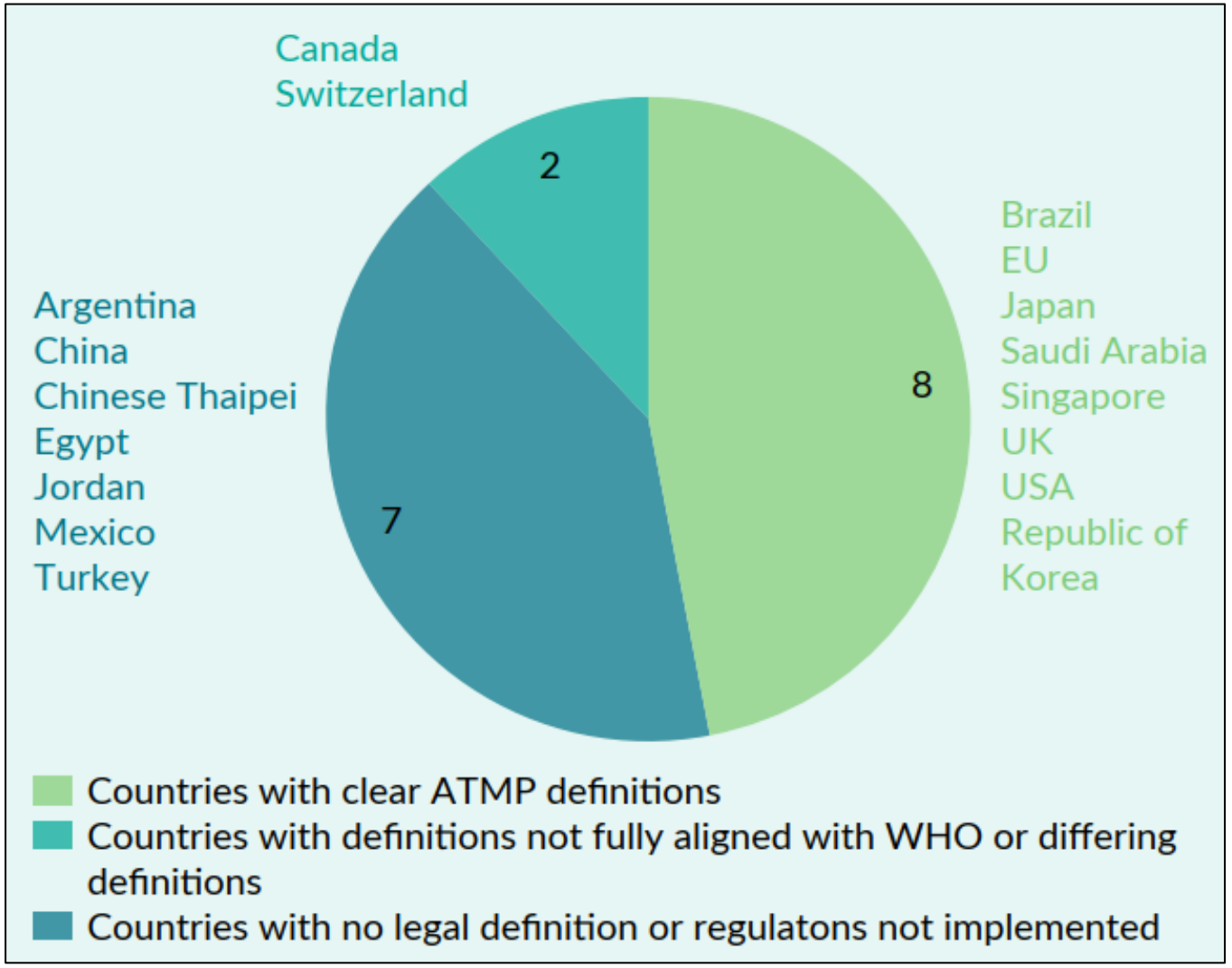
1. Establish clear definitions (i.e., in accordance to definitions established by WHO with corresponding legal/regulatory frameworks) for HCTs and ATMPs.

2. Promote recognition of classification published by reference National Regulatory Authorities (NRA) and identify national authority/institution that will be responsible for product classification and transparent communication of the decisions.



Classification adapted from "WHO considerations on regulatory Convergence of Cell and Gene Therapy Products", 2021.

DEFINITIONS IN ICH MEMBER COUNTRIES (17)



Definitions and terminology for ATMP **not** harmonised across ICH member countries.

TERMINOLOGY USED IN ICH REGULATORY MEMBER COUNTRIES REGULATIONS

ICH member country	Terminology	Product categories
Brazil, Europe, Saudi Arabia, Switzerland, UK	ATMP	Brazil: advanced cellular therapy products, tissue engineered products and gene therapy products [10] Europe: somatic cell therapy, gene therapy, tissue engineered and combined ATMP [11] Saudi Arabia: same as Europe [12] Switzerland: besides somatic cell therapy products, tissue-engineered products, and gene therapy products, ATMP also includes DNA oligonucleotide, antisense RNA, and vaccines [13] UK: same as Europe [14]
Singapore	CTGTP	Cell therapy, gene therapy, tissue engineering, combined CTGTPs [15]
USA	Regenerative medicine therapy; biological products	Cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products [16]
Chinese Taipei, Japan	RMP	Chinese Taipei: products containing genes, cells, and their derivatives intended for human use [17] Japan: cell therapy, gene therapy, tissue engineered [18]
The Republic of Korea	ABP	Cell therapy, gene therapy, tissue engineered and combination products [19]
Canada	ATP	ATPs are products that do not fit within Health Canada's existing regulations; they can be either drugs, medical devices, or any combination of both; currently ATP includes fecal microbiota therapy, adaptive machine learning-enabled devices [20,21]
Argentina, China, Egypt, Jordan, Mexico, Turkey	No ATMP specific terminology; existing national frameworks for biologics are applied	N/A

ABP: advanced biopharmaceutical products. ATMP: advanced therapy medicinal products. ATP: advanced therapeutic products. CTGTP: cell, tissue, and gene therapy products. ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. RMP: regenerative medicine products.

IFPMA POSITION 2023 PAPER RECOMMENDATIONS 3 - 6

REGULATORY RECOGNITION AND RELIANCE ACROSS THE PRODUCT LIFECYCLE

The World Health Organisation (WHO) defines:

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

NRA: National Regulatory Authority.

WHO. Good reliance practices in the regulation of medical products: high level principles and considerations. 2021

RECOMMENDATIONS

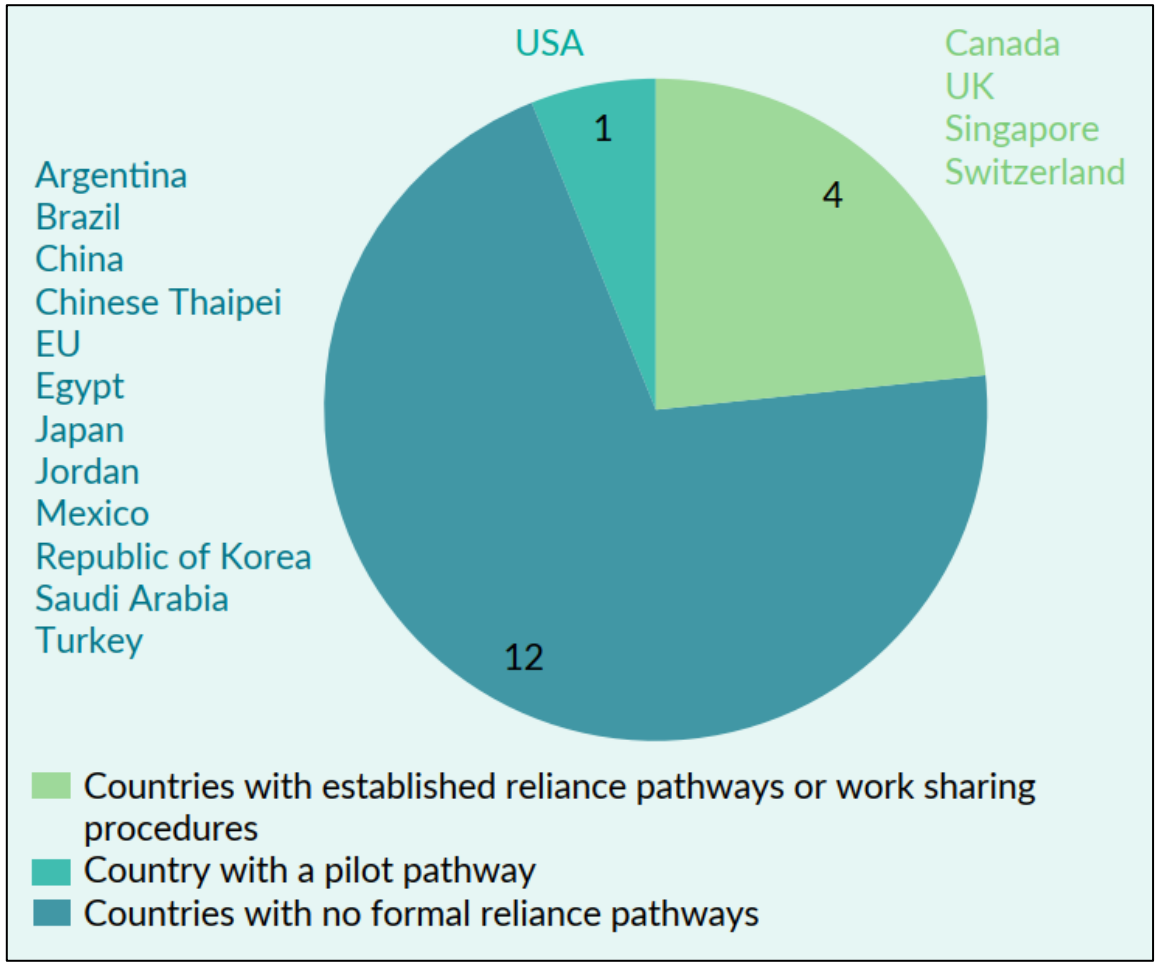
3. Enable recognition and reliance approaches across the lifecycle of ATMPs. This should include products approved through expedited regulatory pathways.

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

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

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

RELIANCE AND WORK-SHARING PROCEDURES FOR ATMPS



Recommended to facilitate reliance, recognition and collaboration across lifecycle of an ATMP.

- 2023 **ACCESS Consortium** expanded scope to include ATMPs:
  - Harmonise regulatory approaches across Australia, Canada, Singapore and Switzerland.
- 2024 **FDA CoGenT (Collaboration on Gene Therapies) Global Pilot**:
  - Exploring potential for concurrent, collaborative reviews of new gene therapy applications with other regulatory bodies: EMA, FDA, PMDA, Health Canada and Swissmedic.
- Singapore: CTGTP can qualify for abridged evaluation if already received approval from one of HSA's comparable regulators.
- UK MHRA implemented International Recognition Procedure: allows MAA for products, including ATMPs, if authorised by designated reference regulators.
- Pathways designed to *expedite* product approvals:
  - US Regenerative Medicine Advanced therapy (RMAT) designation
  - SAKIGAKE designation in Japan.
  - PRIME (Priority Medicines) scheme in Europe.

PROMOTING GOOD REGULATORY AND RELIANCE PRACTICES

Good regulatory practices

Set of principles and practices applied to the development, implementation and review of regulatory instruments in order to achieve a public health policy objectives in the most efficient way

Addressing responses to **common gaps in regulatory practices** identified during benchmarking of national regulatory systems

Relevant to all regulators, irrespective of resources, maturity or regulatory models (national, supranational and multiple institutions)

Annex 11: Good regulatory practices in the regulation of medical products (March 2021)

Good reliance practices

The act whereby the regulatory authority in one jurisdiction takes into account and gives significant weight to assessments performed by another regulatory authority or trusted institution, or to any other authoritative information in reaching its own decision.

Importance of **international cooperation** to ensure the safety, quality and efficacy or performance of locally used medical products

Make best use of available resources and expertise, avoid duplication and concentrate regulatory efforts and resources where most needed

Annex 10: Good reliance practices in the regulation of medical products (March 2021)

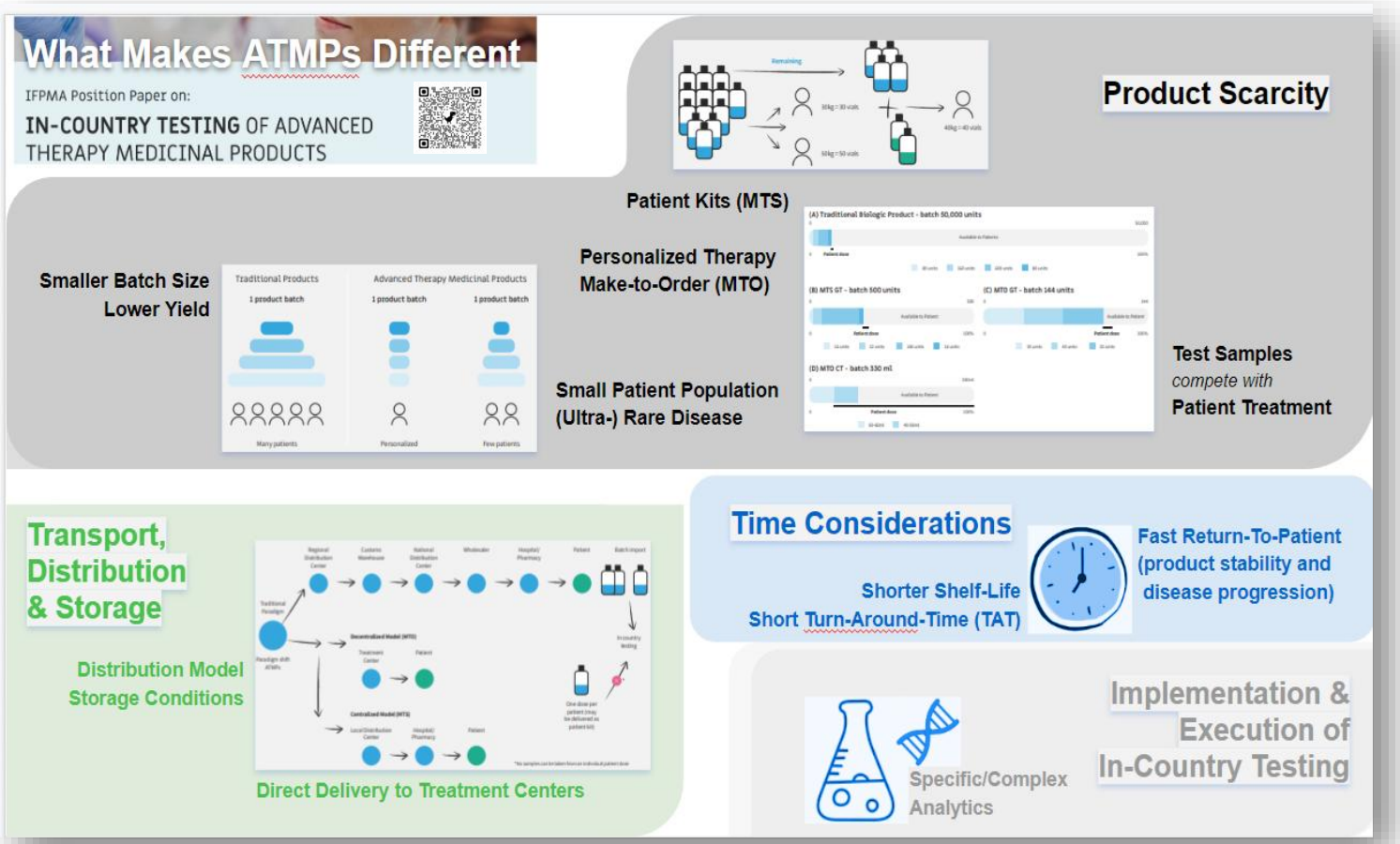
World Health Organization

IFPMA

WHO presentation 2024 CASSS NA CMC Forum

IN COUNTRY TESTING - OVERVIEW

- Secondary quality control of traditional pharmaceutical products required in several markets.
- In-country quality control is performed for:
  - **Registration testing**, including lifecycle management (new registrations, license renewals, line extensions, post-approval changes).
  - **Import testing** (including lot release testing of vaccines and blood products).



IFPMA POSITION 2023 PAPER RECOMMENDATIONS 7 - 9

EXAMPLES OF ACCESS-LIMITING REQUIREMENTS

SUPPLY, QUALIFICATION OF COLLECTION CENTERS AND IN-COUNTRY TESTING

- Chain-of-Custody and Chain-of-Identity allow end-to-end product traceability from the collection (e.g., blood, tissue, cells) to product administration.
- Due to the lack of harmonisation in regulatory requirements, manufacturers apply own standards, leading to different approaches regarding certification, onboarding, audit, and management of collection sites:
- Non-harmonized approach leads to redundancies, and unnecessary administrative burden for biospecimen collection sites, pathology labs, or treatment centers.
- **Burden could be reduced by converging existing regulation and recognition of existing fit-for-purpose regulations and accreditations**, specific to the field of cell, blood and tissue collection and handling.

> **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.

- Given the specific supply chain process, country-specific requirements such as sampling or in-country testing, etc, could jeopardize product integrity, collection or distribution, and delay or prevent patient access to ATMPs.
  - **Recommendation to waive in-country testing and rely on CoA, etc.**

RECOMMENDATIONS

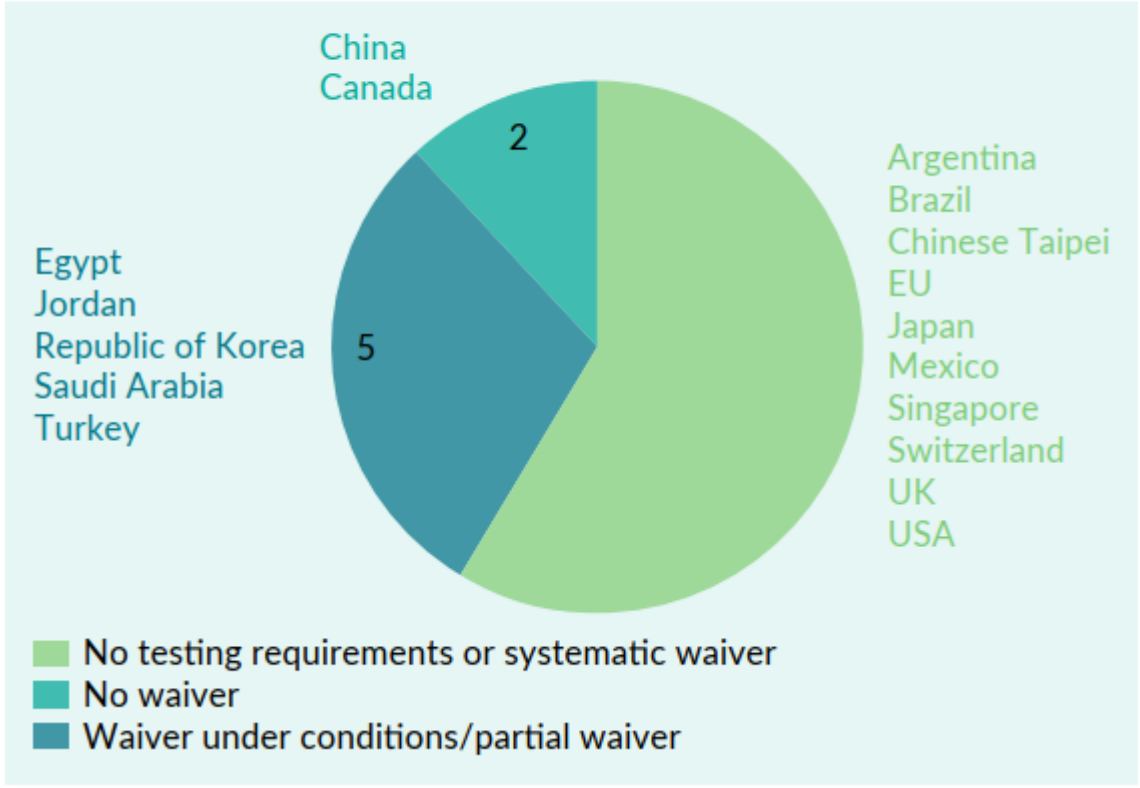
7. Promote convergence of existing regulation (requirements and interpretation) and recognition of existing fit-for-purpose regulations and accreditations specific to the field of cell, blood and tissue collection/handling (e.g., FACT, JACIE).

8. Encourage global coordination on accreditations and standardization by an international institution (such as the WHO and Standards Coordinating Body.

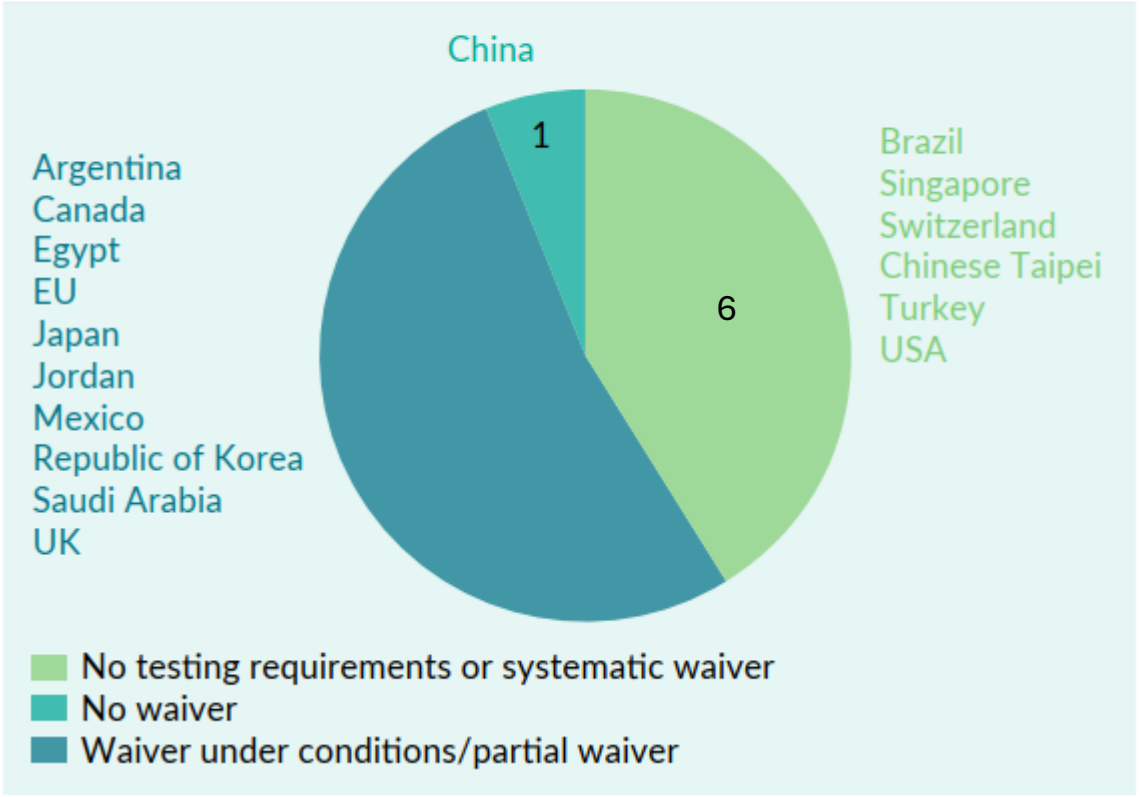
9. Waive in-country testing and rely on Certificates of Analysis (CoA) for products manufactured in facilities certified by reference National Regulatory Authorities (NRA).

IN COUNTRY TESTING - FINDINGS

In-country quality control performed for registration testing in ICH member countries.



In-country quality control performed for import testing in ICH member countries.



Discretionary nature of conditional or partial waivers leads to uncertainty whether testing is required:
Companies typically implement testing in those countries until end of the registration process.

IN COUNTRY TESTING – IFPMA RECOMMENDATIONS

- **Apply waiver schemes** based on reliance on product approvals and inspections from mature National Regulatory Authorities (NRAs).
- Mature NRAs refers to WHO-listed authorities.
- **Rely on CoA's** issued by manufacturers in facilities inspected by mature NRAs:
  - Provides evidence that product manufacturing, testing, and storage/distribution systems are well controlled, validated and comply with current GMP/GDP;
  - Has implemented a proper Quality Management System to ensure compliance;
  - Is under regular control of independent auditing and globally recognized inspectorates (e.g., such as PIC/S members or other competent NRAs).

ATMP LABELLING

- ATMP products require specialized labelling that addresses their biological nature, patient-specific applications, and complex manufacturing processes.
- Challenges:
  - Ultra-low temperature storage requirements;
  - Country-specific regulatory compliance across different jurisdictions;
  - Ensure traceability through unique identifiers while maintaining patient privacy;
  - Labels must convey comprehensive safety information, handling instructions, and product characteristics despite space limitations;
  - System needs to support real-time manufacturing environments and distributed clinical settings.

- See EuroCGT - Packaging and labelling of ATMPs for further information.

IFPMA POSITION 2023 PAPER RECOMMENDATIONS 10 & 11

- Country-specific labels are typically required.
- ***Challenging*** for ATMPs, as typically stored at ultra-low temperatures, with primary label often applied to vial or cryobags, prior to freezing:
  - *Label could be applied prior to freezing; however, country-specific labelling limits flexibility for allocating products on demand and may result in discarding high-cost products that have the wrong country-specific labels.*
  - *Label could be applied on vial or cryobag after thawing and drying; however, this introduces an unnecessary freeze-thaw cycle which could impact stability and the shelf life.*
  - *Label could be applied to the frozen vial or cryobag, but the logistics are complex and labels may lose adhesiveness over time.*
- (No satisfactory method currently for labelling primary container).
- Use of reliance pathways also important, since would ensure content is aligned with reference market across product lifecycle.

UNIVERSAL LABELS

RECOMMENDATIONS

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

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

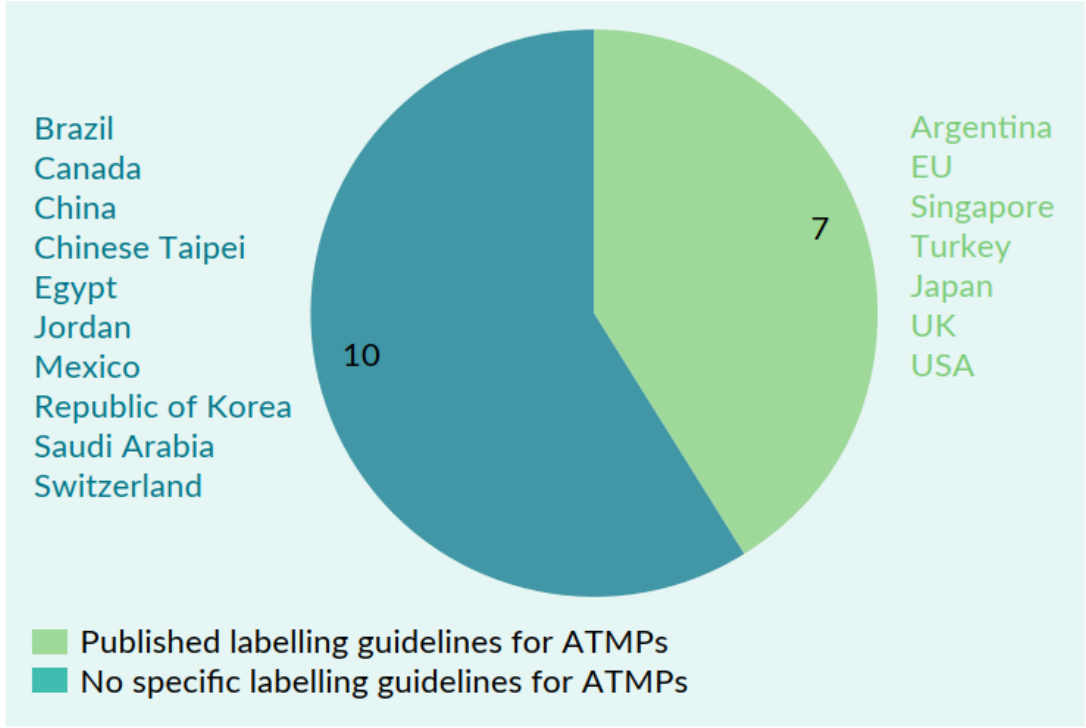
EMA/493897/2015 Rev. 1: Mobile scanning and other technologies in the labelling and package leaflet of centrally authorised medicinal products

ATMP LABELLING – INFORMATION STANDARD FOR BLOOD AND TRANSPLANT 128

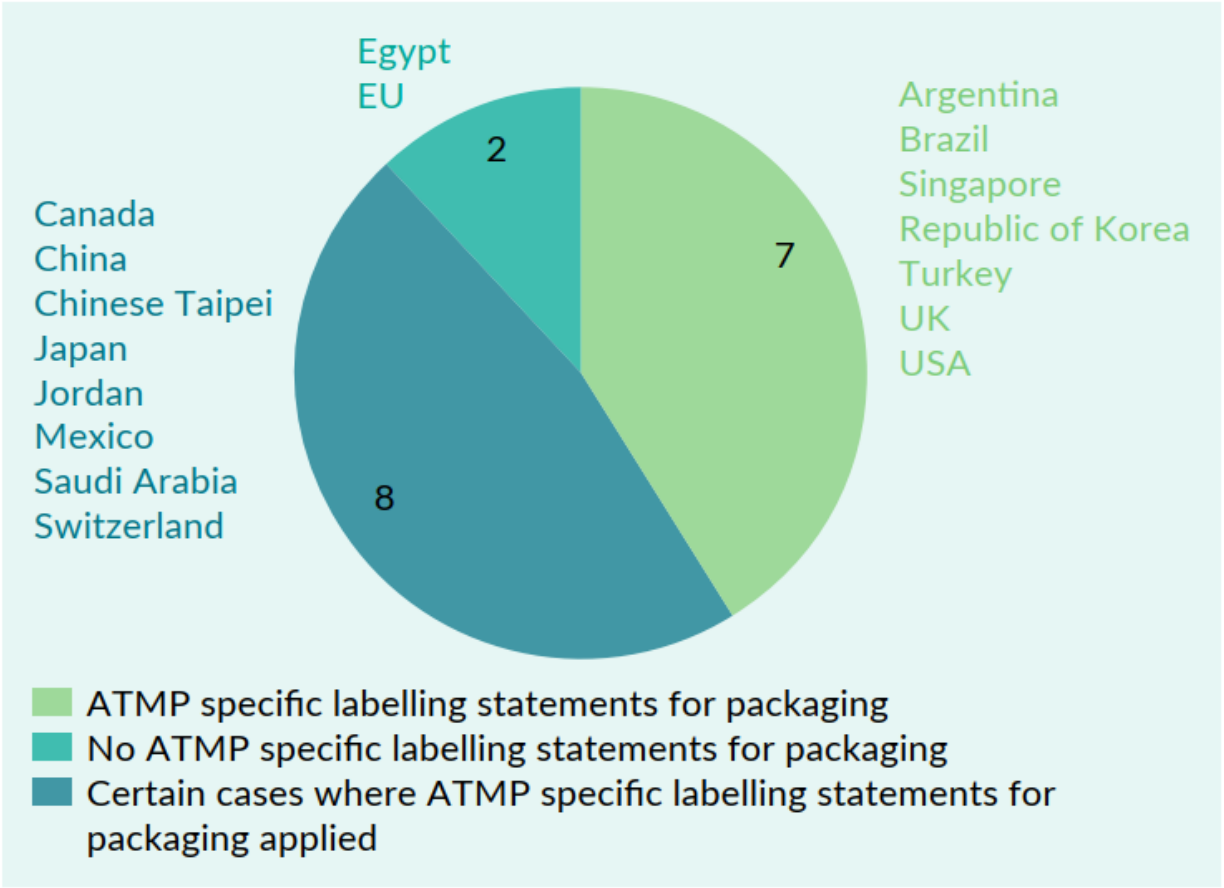
- IFPMA focused on availability of guidelines for ATMP labelling, international standards for track and trace, such as ISBT128, use of digital technology for e-labelling, and language requirements.
- **ISBT 128** an international standard for identification, coding, labelling, and information transfer of human blood, cell, tissue, and organ products.
    - Provides globally unique donation numbering system, standardised product codes, and data structures for barcoding and electronic data interchange,
        - Ensures accuracy, safety, and efficiency across international borders.
    - 13-character unique donation identifier and supports machine-readable bar codes, such as Code 128 and Data Matrix symbols.
    - Managed by ISBT128 Standard for Traceability (a non-profit organization).
    - Widely adopted worldwide for improving traceability and patient safety in transplantation and transfusion.

ATMP LABELLING & PACKAGING

Published labeling guidelines for ATMPs.

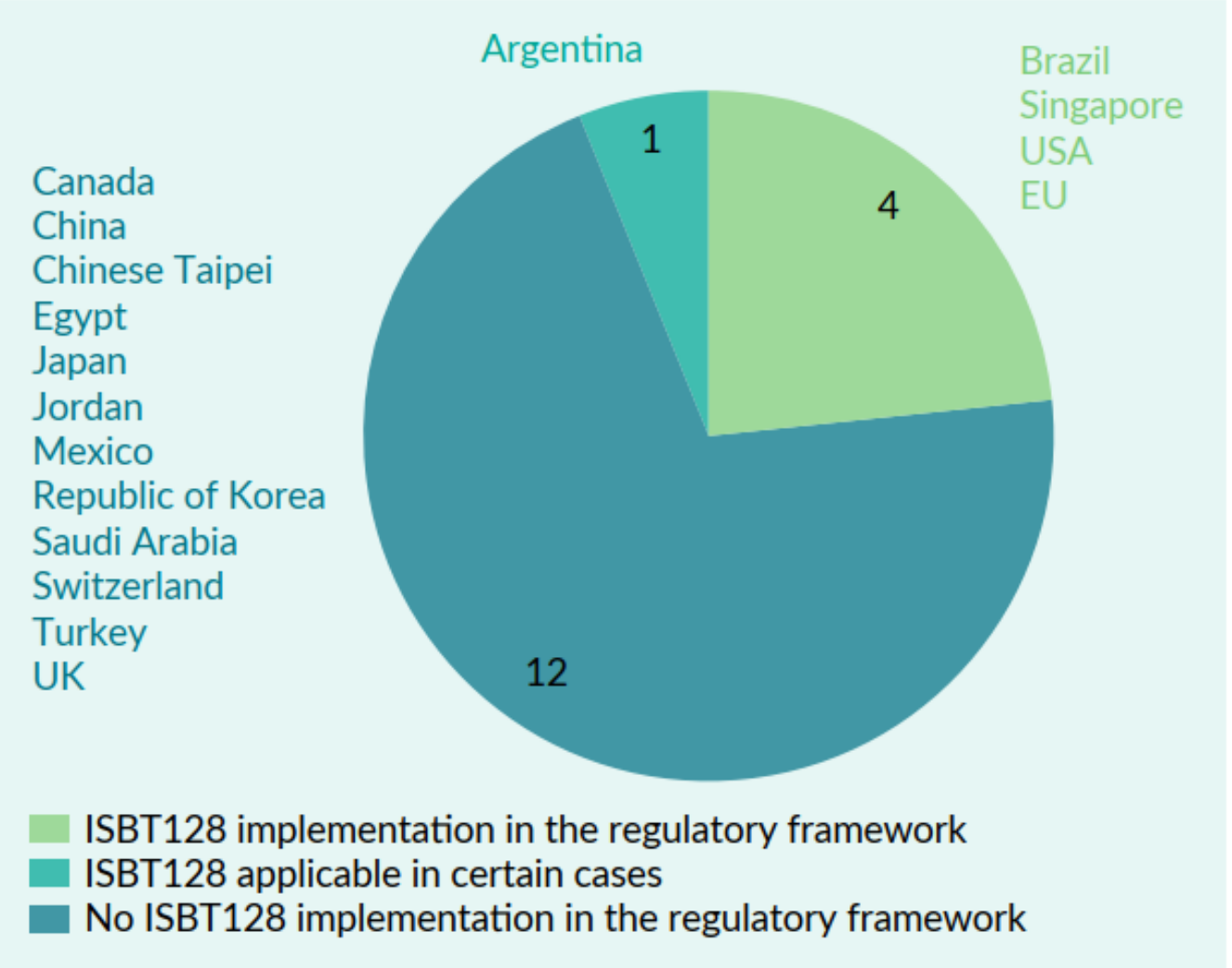


Distinction between countries that mandate specific statements on ATMP packaging.



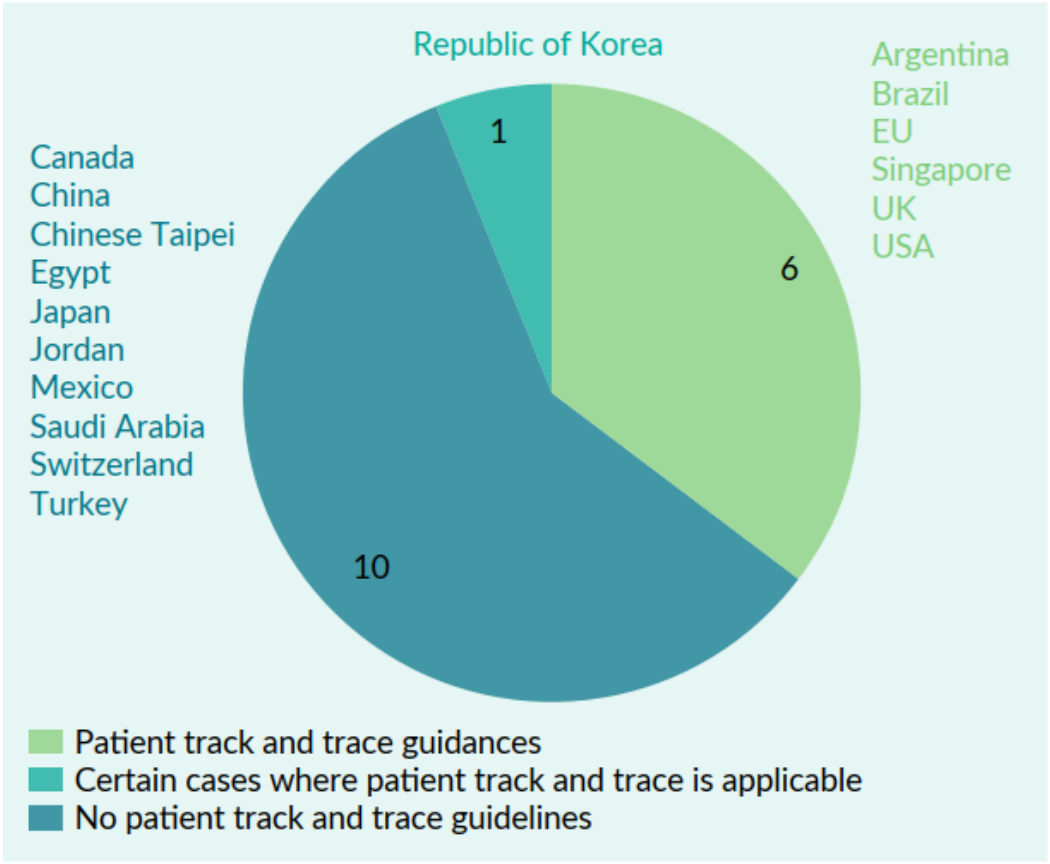
GLOBAL IMPLEMENTATION OF ISBT128 FOR ATMPS WITHIN NATIONAL REGULATORY FRAMEWORKS

ISBT 128 is an international standard for the identification, coding, labelling, and tracking of medicinal products of human origin.

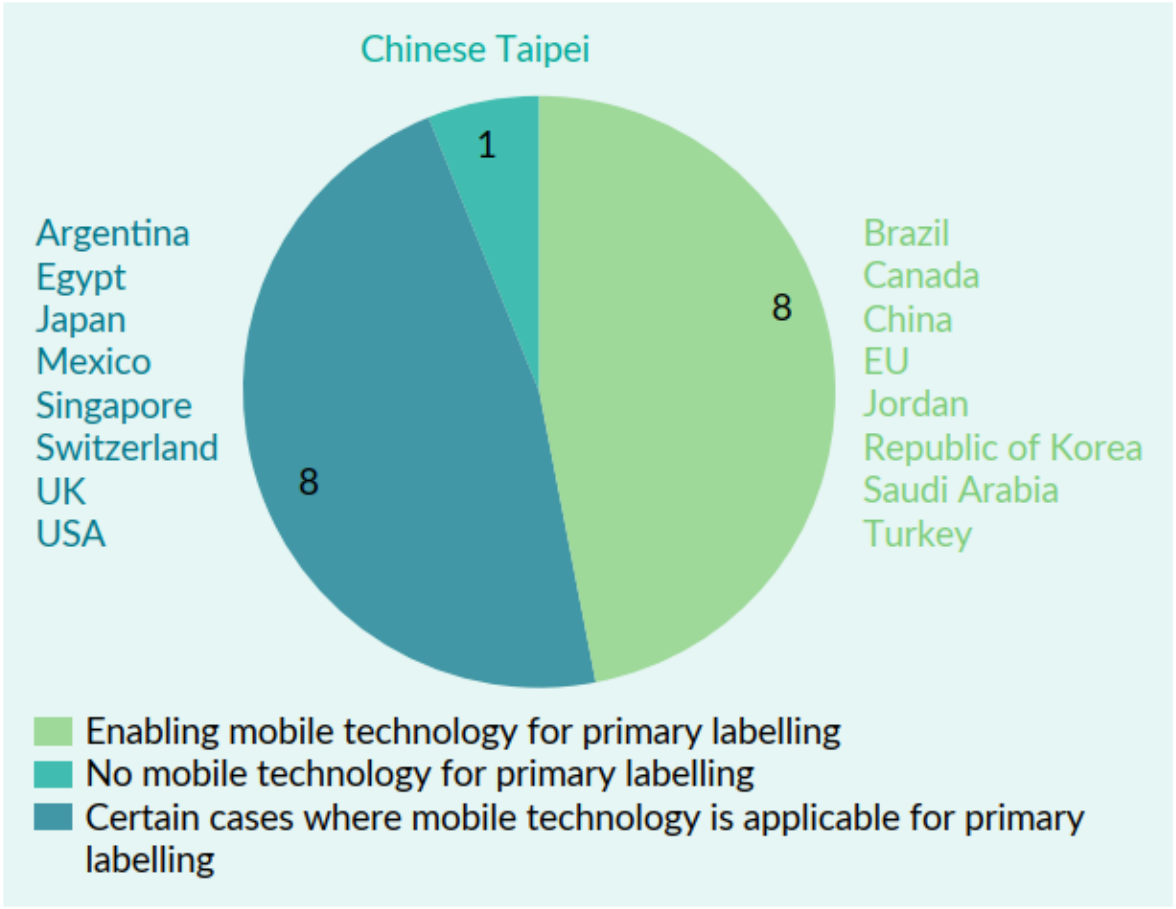


PATIENT TRACK AND TRACE MECHANISMS FOR ATMPS

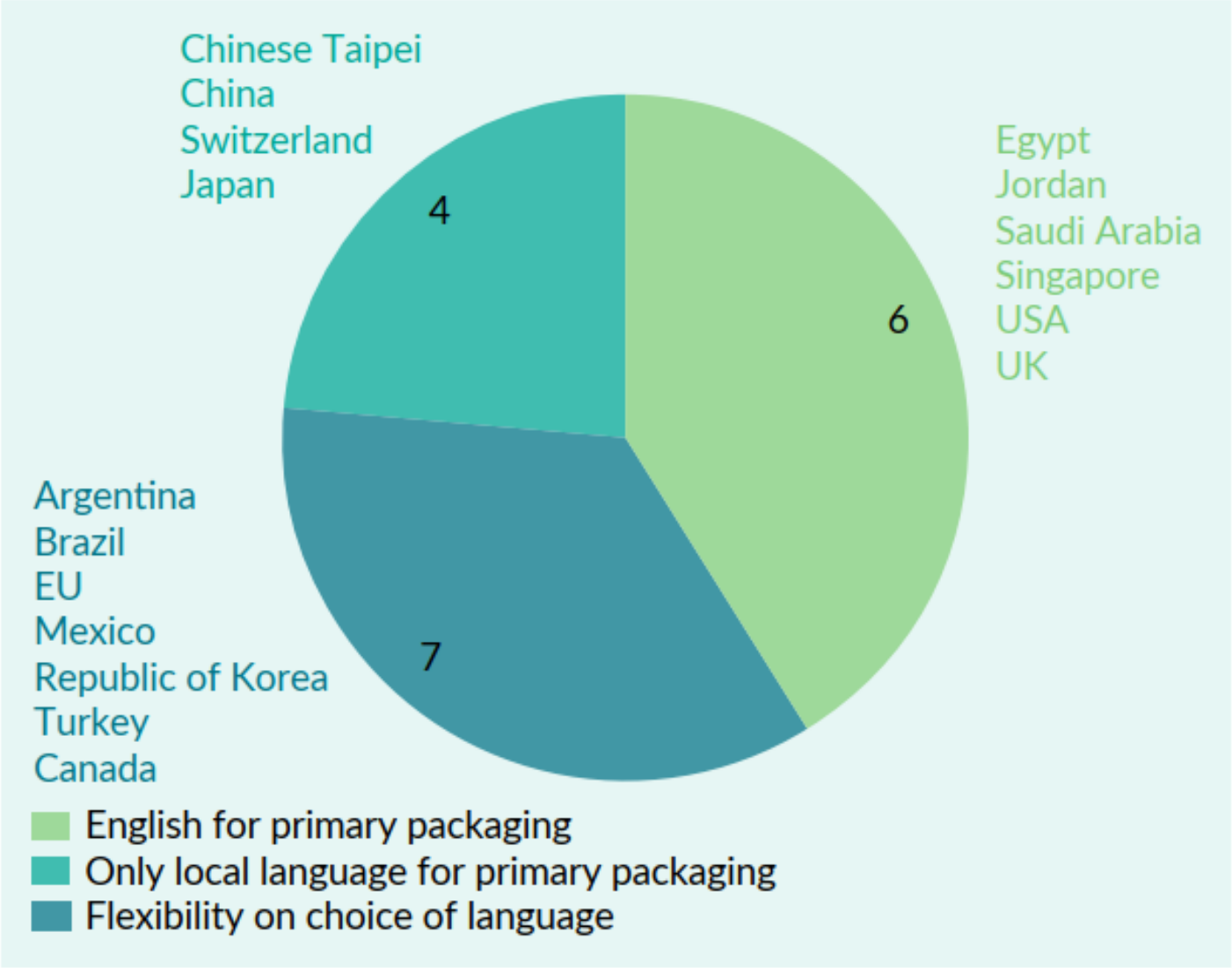
Patient track and trace mechanisms for ATMPs in ICH member countries.



Diversity in regulatory approaches to digital innovation in labeling practices.



ATMP LANGUAGE REQUIREMENTS FOR PRIMARY PACKAGING



IFPMA RECOMMENDATIONS FOR LABELLING OF ATMPS

Broaden implementation of international standards:

- Regulatory agencies should consider developing harmonized labelling standards for ATMPs, or consider the adoption of ISBT128, to facilitate traceability, improve patient safety, and support global distribution of ATMPs.

Develop tailored and adaptive regulatory frameworks:

- Legislation and guidance should incorporate specific provisions for the unique requirements of ATMPs, including considerations for ultra-low temperature storage and the durability of label materials.

Enable flexible labelling approaches:

- Allow for adaptable language and content on primary and secondary packaging to address multilingual markets and reduce barriers to access, while ensuring the clarity and accuracy of product information.

Leverage digital technologies:

- The integration of mobile technologies (e.g., QR or 2D matrix codes) should be encouraged to provide real-time access to electronic product information, enhance track-and-trace systems.

IFPMA POSITION 2023 PAPER RECOMMENDATION 12

GMP STANDARDS AND INSPECTION

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

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

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

RECOMMENDATIONS

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

PIC/S Annex 2A 'Manufacture of Advanced Therapy Medicinal Products for Human Use'

IFPMA POSITION 2023 PAPER RECOMMENDATIONS 13-15

GENETICALLY MODIFIED ORGANISM (GMO) REQUIREMENTS

- In many regions, GMO regulations primarily established for agricultural applications.
  - GMO risk assessment requirements for deliberate release of GMO plants do not appropriately reflect the low risk to the environment for ATMPs in clinical trials.
- The regulation of GMO ATMPs is highly fragmented across regions, particularly at clinical trial stage.
- Differences in expectations and processes for GMO environmental risk assessments (ERAs) of GMO ATMPs result in a high regulatory burden and potential delays to initiation of clinical trials, as reported for the EU.

RECOMMENDATIONS

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

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

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

ADJACENT TO CLINICAL TRIAL APPLICATION, GMO APPLICATION REVIEW TIMEFRAMES IN ICH REGULATORY MEMBER COUNTRIES

- FDA allows 'categorical exclusion' for clinical studies with gene therapies, exempting them from ERA requirements for INDs

Country	Timeframe	Comments
Brazil	8–10 months	5 months if urgent review requested
Canada	120 days	Intended efforts to align assessment period to match CTA 30 days review period
European Union	15–165 days	Variable depending on member state; review within 30 days observed in some countries (e.g., France, Belgium, and Portugal)
Japan	≥3 months–6 months	If human cells are genetically modified cells using recombinant viruses of the family Retroviridae (gammaretroviruses and lentiviruses, designed so that replication-competent recombinant viruses are not easily generated) and if it can be demonstrated that the final product does not contain residual active vector, then a GMO/LMO (living modified organism) exemption can be claimed [38,39]
UK	45–100 days	For low hazard, class 1 (such as rAAV): final clearance within 45 days; however, if the clinical site has prior contained use notification, no further notification is required Class 2: up to 55 days without prior notification; up to 10 days if prior site notification Class 3-4: up to 100 days without prior site notification; up to 55 days if prior site notification
China, Chinese Taipei, Egypt, Mexico, Republic of Korea, Singapore*, and Turkey	N/A	No regulatory framework specific to ATMPs containing GMOs *Genetic Modification Advisory Committee recommendation is required adjacent to a CTA for a CTGTP (in Singapore).

GMO ATMP'S WITHIN EUROPEAN UNION (EU)

Four industry surveys across EU:

- 2021, GMO approval timelines reported to be highly variable, often within the same EU Member State.
    - 32% of GMO approvals granted *after* approval of the CTA.
- 2023, highly variable timeframes with differences in adaptation to timelines dictated by EU Clinical Trials Regulation (CTR).
    - 60% GMO applications delayed initiation to clinical trial.
- 2025, 90% report that no alignment across review timelines for a GMO application and CTA.
    - Misalignment caused delays to the start of clinical trials in 44% cases.
- 2026: Review timeframes even longer, irrespective to whether Member State transposed Directive for Contained Use and/or Deliberate Release.

Simplification anticipated…2027 - 2028…

- Revision to EU General Pharmaceutical Legislation: **ERAs to be assessed centrally** by the EMA's Committee for Medicinal Products (CHMP) for Human Use, with single review timeframe
- European Biotech Act proposes to **exempt** investigational GMO ATMPs from ERA, *if* pose no or negligible risks.

GMO ATMPS RECOMMENDATIONS

- Lack of reliance or recognition procedures for GMO IMP authorisation prior to, or in parallel to a CTA.
  - Despite no formal reliance mechanism, Brazil informally recognised European GMO approvals.
- No single definition of GMO (or Living Modified Organism) applied across all regions.
  - Lack of clarity e.g., Viral Replicon Particles, saRNAs.
- **Recommended to:**
  - Develop global or **universal common application** forms for GM cells & viral vectors
    - Minimize duplication of efforts.
- International regulators **foster reliance** or develop a legal framework for GMO ATMPs:
  - Recognition and reliance pathways could be explored based upon Cartagena Protocol on Biosafety and its supplementary protocol on liability and redress.

HOSPITAL EXEMPTION – OVERVIEW: EU

- Lack of internationally standardised regulatory mechanisms to support provision of unlicensed cell, gene, or tissue therapies to patients with unmet medical needs.
- Article 28(2) of the EU ATMP Regulation No 1394/2007, as implemented in Article 3(7) of Directive 2001/83, introduces the **Hospital Exemption scheme**, empowers Member States to permit the provision of an ATMP, without marketing authorization, under certain conditions. Products must be:
  - prepared on non-routine basis;
  - prepared in accordance with specific quality standards;
  - used within a single Member State;
  - used in a hospital setting, under the exclusive professional responsibility of a medical practitioner;
  - prepared to comply with a medical prescription for a custom-made product for an individual patient.
- EU Member States must authorize the manufacturing of these products and ensure manufacturing quality standards are met.
- EU Member States must also ensure traceability and pharmacovigilance requirements are met.

HOSPITAL EXEMPTION (HE) IN ICH COUNTRIES

- For countries with provisions, both Health Authority approval and GMP (or equivalent) compliance are most common requirements.
- Japan: As well as PMDA approval, the manufacturing standards share the same principles as good gene, cellular, and tissue-based products manufacturing practice (GCTP) or GMP.
- UK: Product to be used under HE is not directly approved by MHRA, but manufacture must be conducted to GMP.
- USA: No provision under HE pathway. Access to unlicensed products via IND pathway.
- Canada: Equivalent to HE scheme does not exist, but alternative pathway via the Special Access Program for Drugs.
- Switzerland: No formal implementation of an equivalent to HE. Manufacture of unlicensed products in a hospital pharmacy under a manufacturing license is allowed, and relevant legislation is under review.
- Republic of Korea: Since February 2025, allows patients with severe, rare, or incurable conditions to receive CGTPs that do not have market approval.
- Chinese Taipei and Saudi Arabia do not have specific provisions.
- Overall, the processes and requirements differ from country to country (including across EU).

HOSPITAL EXEMPTION – IFPMA RECOMMENDATIONS

- Foster collaboration, convergence, and ultimately consistency among regulators across hospital exemption, or equivalent schemes, to facilitate access to unlicensed ATMPs:
  - Allows individual patients being able to access treatment where an urgent unmet clinical need
  - when no available product on the market in territory, or no opportunity to take part in a suitable clinical trial;

- Encourage establishment of internationally aligned and robust regulatory pathway
  - Facilitate commercial and non-commercial product development via appropriately robust and regulated pathways, according to established licensing routes for evidence generation:
  - Avoids dual pathways with different quality, safety, and efficacy standards.

CONCLUSIONS & OPPORTUNITIES

- Diverse nature of ATMPs necessitates regulatory frameworks that are flexible and adaptable to accommodate unique characteristics.
- (per WHO, 2021) to foster unilateral **reliance** and **recognition** approaches, avoid duplication of efforts, and encourage efficient resource utilization, *there is need for:*
  - (per WHO, 2023) **Convergence** of regulatory approaches (e.g., definition of products, classification, regulatory requirements):
    - Embrace reliance and work-sharing procedures.
  - Waiving in-country testing for ATMPs:
    - Rely on CoAs issued by manufacturers operating in facilities approved and inspected by mature NRAs.
  - Standardized approaches for GMO ERAs: Universal application forms.
  - Convergence on labelling requirements: Continued collaboration among regulatory authorities.
- Implementation of consistent and internationally aligned regulations for hospital exemptions is essential to allow access personalized, unlicensed ATMPs.
- Continued collaboration among regulatory authorities and WHO paramount to develop *fit-for-purpose* ATMP regulations and requirements.
  - Lack of clear and predictable regulatory frameworks for post-approval changes for ATMPs in Latin America.

IFPMA

Advanced Therapies Working Group

Including:

An analysis of advanced therapy medicinal products regulatory landscape in ICH member countries: opportunities and challenges

Srinivasan Kellathur, Joerg HO Garbe, Stuart G Beattie, Martin O'Kane, Anna Litsiou, Kowid Ho, Sarah Adam, Srikanth Muralidharan, and Mustafa Hussain

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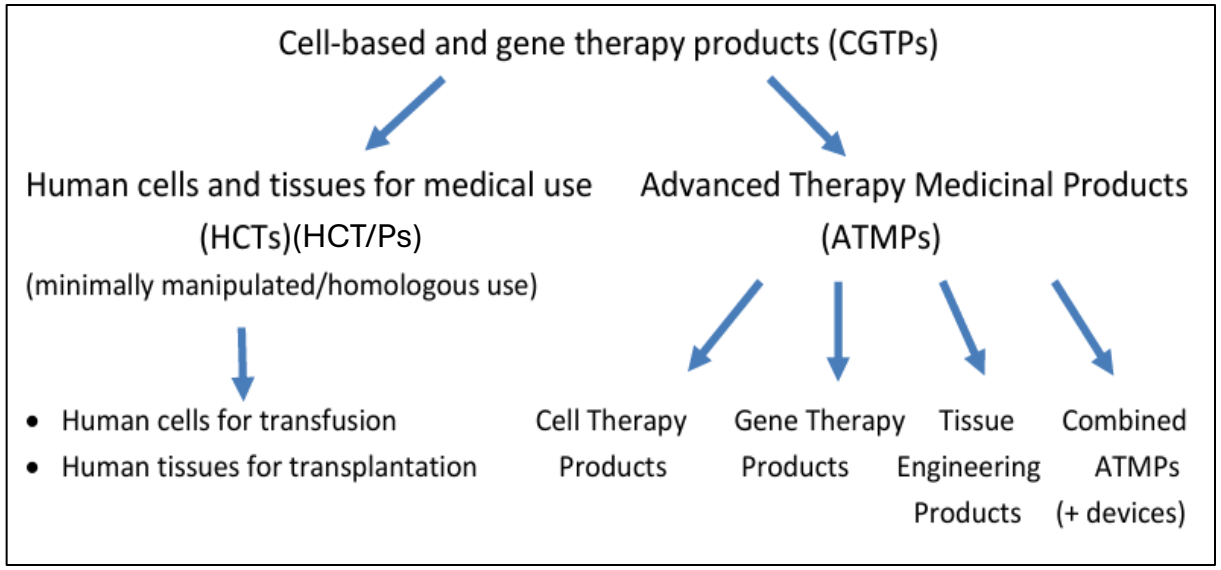
Biogen

WHO 2021 CONSIDERATIONS DOCUMENT

World Health Organization

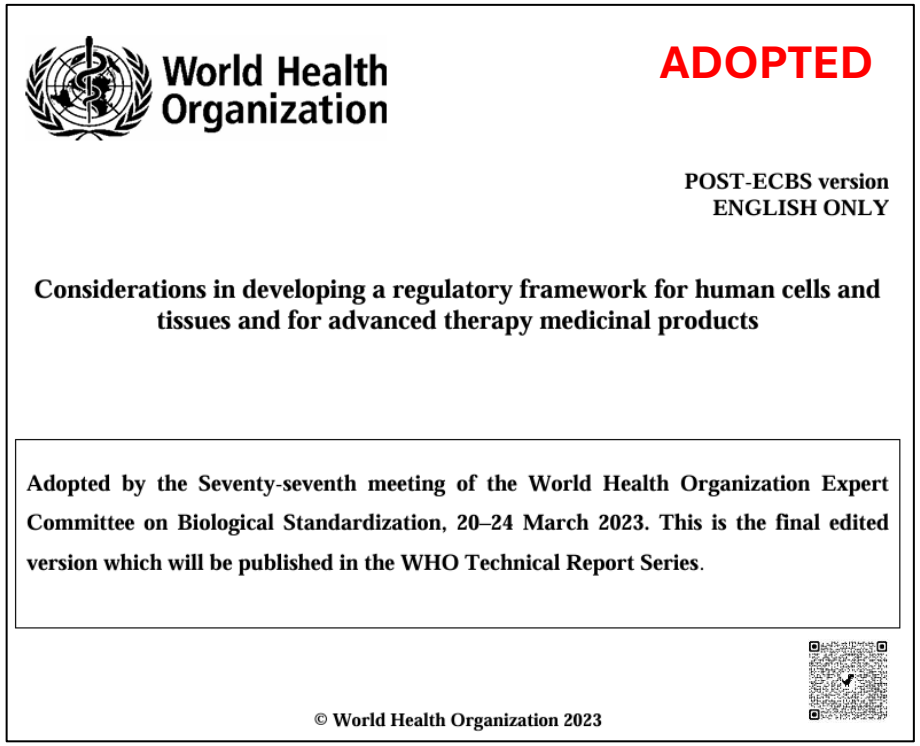
WHO/CGTPs/DRAFT/16 December 2021
ENGLISH ONLY

WHO considerations on Regulatory Convergence of Cell and Gene Therapy Products



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

WHO 2023 CONSIDERATIONS DOCUMENT (1)



World Health Organization

ADOPTED

POST-ECBS version
ENGLISH ONLY

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

Adopted by the Seventy-seventh meeting of the World Health Organization Expert Committee on Biological Standardization, 20–24 March 2023. This is the final edited version which will be published in the WHO Technical Report Series.

- Facilitate **global convergence among regulators.**
- Provide a set of basic definitions and terminology:
  - **Definition** of an **ATMP** being: ***"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 also include nucleic acids, viral vectors, recombinant bacterial cells and recombinant oncolytic viruses."***
- Classification of Human Cells and Tissues for medical use and ATMPs
  - ATMPs can be sub-categorized according to their degree of processing and their mode of application – factors that directly impact their risks.
- Encourage the establishment of regulatory frameworks in countries where none exist.
- Encourage the use of **regulatory convergence and reliance** to build regulatory capacity and harmonisation between countries and regions.

WHO 2023 CONSIDERATIONS DOCUMENT (2)

Terminology section includes regulatory definitions:

"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."