European Experience with ATMPs

Why Global regulatory alignment matters

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Regenerative Medicine: Regulatory, Legal, and Compliance Challenges for Cell and Gene Therapies
June 8, 2021

FDLI

In this presentation

1. Specific legal framework
2. Route of ATMPs to the EU market
3. EU approved ATMPs
4. Tools supporting innovation to advance patient access
5. Key learnings
6. Multistakeholder Advice

The presenter does not have any conflicts of interest.

Key principles of the EU ATMP legal framework

PROTECTION OF PATIENTS

- Marketing authorisation system ensures that ATMPs given to patients are safe and efficacious
- Assessment by a specialised scientific committee: Committee for Advanced Therapies (CAT)
- Enhanced follow-up of efficacy and safety post-authorisation

SUPPORT INNOVATION AND DEVELOPMENT OF NOVEL PRODUCTS

- Definitions of ATMPs & Classification
- Risk-based (pragmatic) approach
- Possibility to adapt technical requirements to scientific progress
- Access to conditional MA and other early tools
- Incentives to developers (for example small and medium enterprises)

10.12.2007 EN Official Journal of the European Union L 324/121

REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 13 November 2007
on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004
(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission,

Having regard to the Opinion of the European Economic and Social Committee (1),

After consulting the Committee of the Regions,

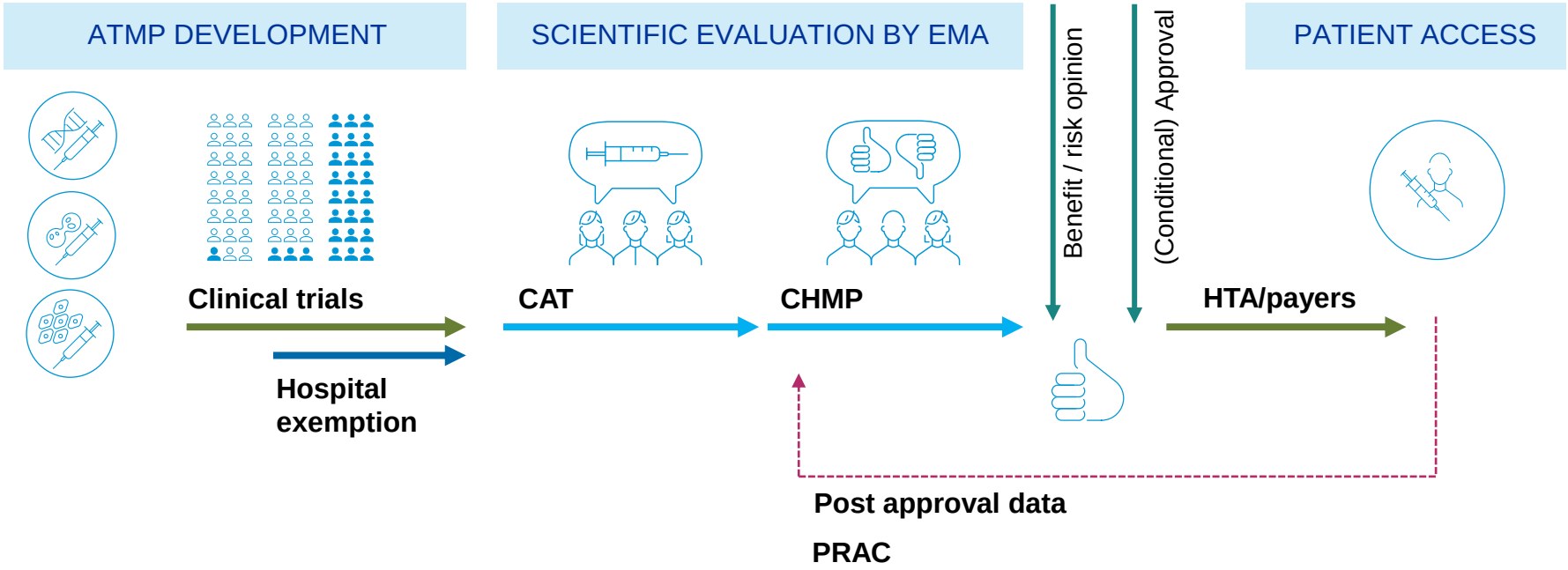
Acting in accordance with the procedure laid down in Article 251 of the Treaty (2),

Whereas:

been defined in Annex I to Directive 2001/83/EC, but a legal definition of tissue engineered products remains to be laid down. When products are based on viable cells or tissues, the pharmacological, immunological or metabolic action should be considered as the principal mode of action. It should also be clarified that products which do not meet the definition of a medicinal product, such as products made exclusively of non-viable materials which act primarily by physical means, cannot by definition be advanced therapy medicinal products.

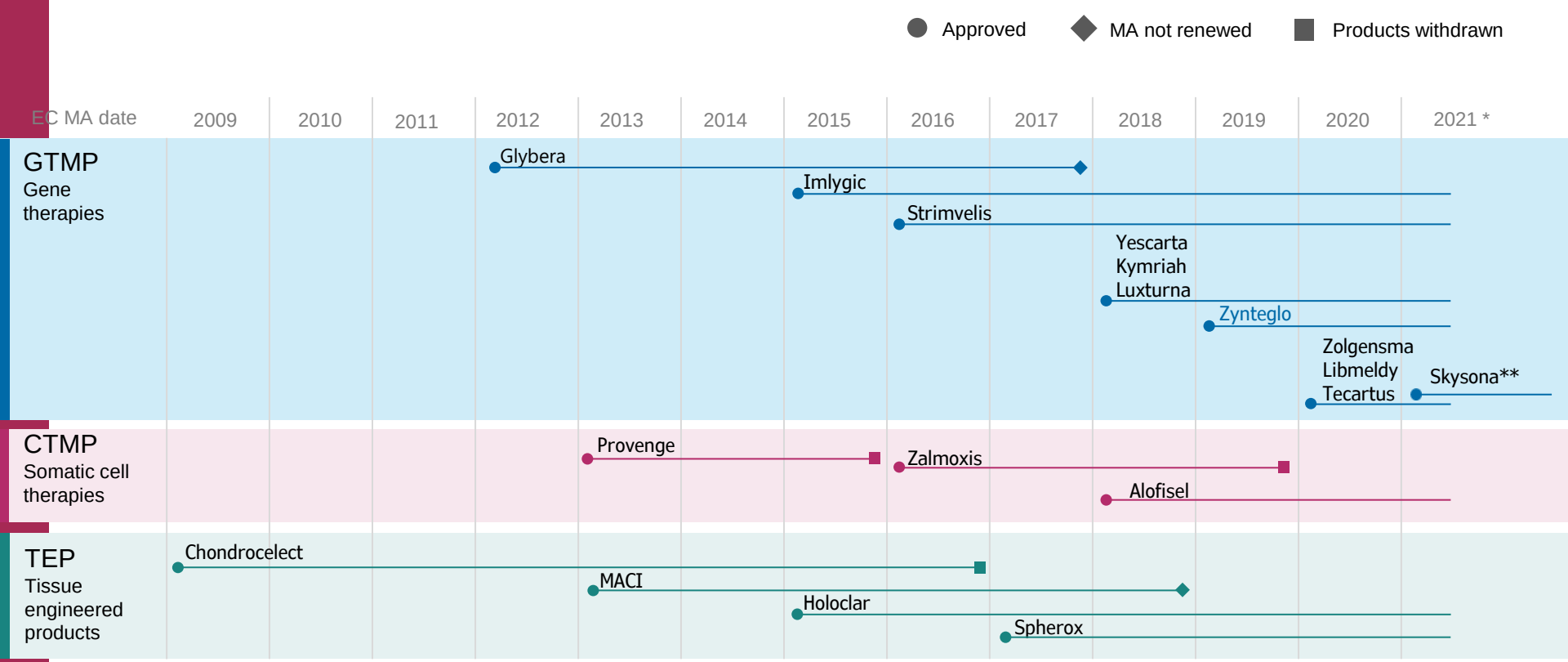
(4) According to Directive 2001/83/EC and the Medical Device Directives the basis for deciding which regulatory regime is applicable to combinations of medicinal products and medical devices is the principal mode of action of the combination product. However, the complexity of combined advanced therapy medicinal products containing viable cells or tissues requires a specific approach. For these products, whatever the role of the medical device, the pharmacological, immunological or metabolic action of these cells or tissues should be considered to be the principal mode of action of the combination product. Such

Entry route of ATMPs to the EU market



CAT: Committee for Advanced Therapies
CHMP: Committee for Medicinal Products for Human Use
PRAC: Pharmacovigilance Risk Assessment Committee

Approved ATMPs 2009-2021



** Skysona: the scientific review has been concluded and the formal Commission decision is pending

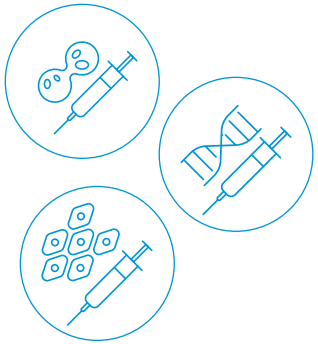
* 6 Ongoing MAA (May 2021)

Ongoing ATMP MAA applications

INN/ Common Name	Therapeutic area	Start of evaluation
Lenadogene nolparvovec	Ophthalmology	29/10/2020
Eladocagene exuparvovec	CNS	28/01/2020
Idecabtagene vicleucel	Oncology	21/05/2020
Autologous glioma tumor cells, inactivated / allogeneic glioma tumor cells, inactivated	Oncology	01/10/2020
Lisocabtagene maraleucel	Oncology	16/07/2020
Ciltacabtagene autoleucel	Oncology	20/05/2021

Supporting innovation to advance patient access

ATMP specific tools



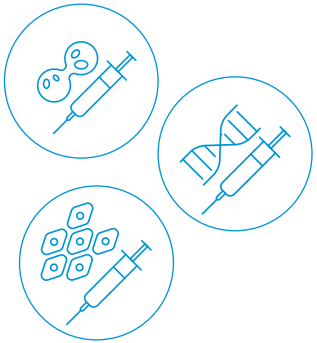
- **Classification** as ATMP
- **Certification** of ATMP quality and non-clinical data for SMEs

Regulatory framework

Early Access

Supporting innovation to advance patient access

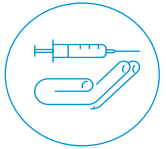
General support



- Innovation Task Force
- Scientific advice
- Parallel advice with FDA/ HTAs
- PRIME (early access)
- Qualification of novel methodologies
- Paediatric and Orphan framework
- Scientific guidelines
- SME support
- Academia cooperation
- Fee incentives
- Quality toolbox

Authorisation

Access decision



Post-licensing evidence

There are many challenges

- Novel technologies:
  e.g. genome editing
- Innovative manufacturing approaches:
  point-of-care manufacturing, release and control
- Borderline products:
  contribution of each component to clinical benefit-risk
- Data requirements:
  small patient populations / comparators / registries
- Evidence generation:
  approval / post-marketing / market access

Learnings from EU experience: critical issues

Quality

- Demonstrated comparability
- Potency testing
- Ensuring product consistency
- Starting material challenges

Nonclinical

- Proof of concept studies
- Design toxicity studies, relevance
- Bridging/comparability studies
- Bio-distribution and shedding
- Non-clinical development data package

Clinical

- Trial design
- Indication/target population
- Dose/regimen
- Primary/secondary endpoints
- Comparator
- Study duration
- Sample size/analysis
- Extent of safety data
- Durability of response

*Towards a better use of scientific advice for developers of advanced therapies", British Journal of Clinical Pharmacology (2020): https://bpspubs.onlinelibrary.wiley.com/doi/10.1111/bcp.14672

Cluster discussions: Regulatory alignment is critical when targeting a small number of patients globally

Under 50 patients In MAA in the EU		Around 100 patients in MAA in the EU	
Skysona	Cerebral adrenoleukodystrophy (CALD)	**Zolgensma**	Spinal Muscular Athropy
Libmeldy	Metachromatic leukodystrophy (MLD)	**Tecartus**	Mantle cell lymphoma
Strimvelis	Severe combined immunodeficiency	**Kymriah**	B cell acute lymphoblastic leukaemia (ALL) and diffuse large B cell lymphoma (DLBCL)
Luxturna	Vision loss due to inherited retinal dystrophy & biallelic RPE65 mutations	**Yescarta**	B cell acute lymphoblastic leukaemia (ALL) and diffuse large B cell lymphoma (DLBCL)
Zalmoxis	Adjunctive treatment to haematopoietic stem cell transplantation (HSCT)	**Holoclar**	Replacement of damaged cells of the cornea
Zynteglo	Beta thalassaemia		

EMA Scientific advice in parallel with FDA

Aligning evidence-generation to serve both agencies

Best candidate products:

→ ***Indications lacking development guidelines***

→ ***If guidelines exist, those for which EMA's and FDA's guidelines differ significantly***

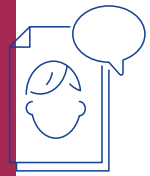
- Early dialogue between regulators and developers
- Clearer understanding of the agencies' respective requirements and perspectives regarding the development program
- Simultaneous feedback on R&D plans
- Harmonisation and increased convergence between EMA and FDA

Scientific advice in parallel with Health Technology Assessment bodies

→ **Aligning evidence-generation to serve both:**

→ ***Approval decisions (EMA)***

→ ***Reimbursement decisions (HTA, national level)***



- **Early dialogue** between regulators, HTAs and developers
- Simultaneous **feedback at an early stage** on R&D plans
- **Optimised development** plan ➔ **Improved access** for patients

Take home messages

ATMP development is complex

- Science evolves faster than regulations
- Multi stakeholder engagement is key to generate optimal evidence for licencing and post licencing
- Regulators talk and you need to talk to us too

Early dialogue with regulators / Scientific advice

- Make use of tools and incentives available to support ATMP development in the EU for pre- and post-marketing evidence generation

Use parallel advice platforms to involve all stakeholders

- ATMPs are ideal candidates for parallel SA with FDA: innovative, challenging development, rare indications lacking regulatory guidance
- Evidence needs to serve global regulators and downstream stakeholders (HTA/payers)

Thank you for your attention

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Further information

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The Path to Harmonization for Cell and Gene Therapies

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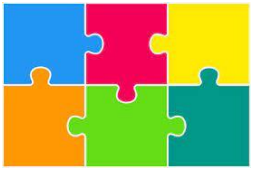
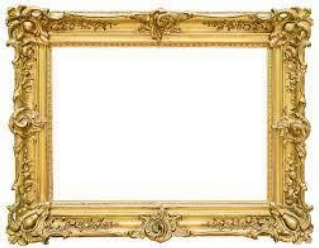
Introduction



- There are multiple puzzle pieces that need to fit together to achieve harmonization for cell and gene therapies
- This reflects a range of challenges due to the diversity of products, the range of the regulatory oversight constructs and competencies, and the pace of scientific understanding
  - Often called “advanced therapies,” these products include cell- and tissue-based products with and without gene modification, viral and oncolytic vectors, genetically modified bacterial vector-based products, tissue-engineered products and more
  - Jurisdictions can vary dramatically in how their legislative and legal frameworks define and regulate these products, if they are regulated at all, and the technical competencies for oversight run the spectrum
  - The scientific knowledge underpinning these products is growing exponentially; the field sees new approaches and new product constructs at an unprecedented pace

Setting the Frame



- “Harmonization” is a term with variable usage
- Narrowly, through the ICH lens – words on paper accepted by all
- More broadly, inclusive of concepts of convergence and alignment
  - Convergence of policy and/or regulatory decisions on specific products may occur in settings of differing legal frameworks; similarly alignment
- **Usage for this presentation:**
  - **Harmonization: mutually accepted guidance wording**
  - **Convergence: comparable policy outcomes despite differing legal frameworks**
  - **Alignment: regulatory outcome on specific product is equivalent or near-equivalent despite differing regulatory framework**

ALL BASED ON A COMMON UNDERSTANDING OF THE SCIENCE!

Acronyms/Glossary

- **APEC/LSIF RHSC:** Asia Pacific Economic Cooperation/Life Sciences Innovation Forum Regulatory Harmonization Steering Committee: Regulatory convergence via implementation/training activities around global best practices and standards (e.g., WHO, ICH, IMDRF)
- **EMA-FDA+ "Clusters":** Under confidentiality arrangements, originally created with EMA alone, expanded over the years to include other confidential partners. Discussion can include policy but most commonly specific product submissions of shared interest to achieve alignment based on scientific principles
- **ICH:** International Council for Harmonisation of Technical Requirements for Pharmaceuticals: an assembly of regulatory and industry experts sharing the goal to harmonize guidelines (agree on one text which regulators commit to implement; original founders: US, EU, Japan but membership now broader)
- **IPRP:** International Pharmaceutical Regulators Programme: information sharing venue for regulators only related to implementation of ICH guidelines as well as broader discussions/work around regulatory convergence. IPRP Management Committee meets at time of the biannual ICH meetings, facilitates the participation of international regulators who also participate in ICH, and supports synergy between the two initiatives
- **PSA:** Parallel Scientific Advice: A structured program between EMA and FDA. A mechanism for reviewers and sponsors to exchange views on scientific issues during the development phase of new medicinal products
- **WHO:** World Health Organization: Broad public health mandate, but specific to FDA related work – develops standards, guidelines, promotes best regulatory practices and convergence

EMA-FDA+ Advanced Therapy “Cluster”

Alignment

“Cluster” discussions

- Under confidentiality arrangements
- Originally created with EMA alone, expanded over the years to include other confidential partners (e.g., Canada, Japan)
- Discussion can include: Guidance under development; Policy perspectives; Clinical trial design & endpoints; Scientific advice; Adverse events; Submissions
- Cell and Gene therapy discussions fall within Advanced Therapy Medicinal Products Cluster primarily, though at times also within Oncology or Rare Disease Clusters; recently ATMP Cluster deemed to be the “home” for all related Cluster discussions

Parallel Scientific Advice (1)

Alignment

- Structured program between EMA and FDA under confidentiality arrangements
- A mechanism for reviewers and sponsors to exchange views on scientific issues during the development phase of new medicinal products
- Optimize product development and avoid unnecessary testing duplication or unnecessarily divergent testing methodologies
- Separate advice given but alignment optimal
- Limited cases in advanced therapies space

Parallel Scientific Advice (2)

Alignment

- Voluntary procedure, at request of sponsor
- Available to sponsors of a future IND, NDA, BLA & MAA (+ supplements & variations)
- Questions on product development put to both FDA and EMA
- Discussions between FDA-EMA, and joint with sponsor
- Each Agency issues separate responses to sponsor‘s questions in line with usual procedures
- General principles: https://www.fda.gov/media/105211/download

IPRP (1)

http://www.iprp.global/home

IPRP
International Pharmaceutical Regulators Programme

- Regulators only information sharing forum with broad goal of convergence
- Among others, working groups on Cell Therapies and separately on Gene Therapies. Both:
  - Share information, best practices, promote regulatory convergence
  - No formal guidance is developed but reflection papers have been written and published
  - Support harmonization initiatives such as APEC and PANDRH
  - Refer topics to appropriate organizations such as ICH, PIC/S, WHO
  - Mandates and workplans on website

Convergence

IPRP (2)

http://www.iprp.global/home

IPRP
International Pharmaceutical Regulators Programme

Cell Therapy Working Group

Scope: Cell and tissue-based products (without gene modification), tissue engineered products, xenotransplantation products

- In 2018, finalized Reflection Paper: "General Principles to Address the Nature and Duration of Clinical Trials Using Cell Therapy Products" (2018)

Gene Therapy Working Group

Scope: Viral vectors, oncolytic vectors, genetically modified bacterial vector-based products, genome editing technologies

- In 2018, finalized Reflection Paper: "Expectations for Biodistribution Assessments for Gene Therapy Products" →→ foundation for current ICH S12

Both WGs work together at times when overlapping issues/work - Currently updating previous regulatory landscaping document to reflect current state-of-play in regulatory frameworks of members

Convergence

APEC RHSC (1)

apec.org/rhsc

Regulatory Harmonization Steering Committee

APEC

Life Sciences Innovation Forum

- A platform for promoting regulatory convergence, capacity and cooperation in areas relevant to medical product regulation
- Participants:
  - Regulators from APEC Economies
  - Industry coalitions (Research-based Pharmaceuticals; Medical Devices; Generic Pharmaceutical; Biotechnological Products; Advanced Therapies)
  - Academia
- Does not produce harmonized guidances. Promotes training, implementation and use of internationally-recognized guidelines and best practices in Priority Work Areas, including Advanced Therapies
- Employs Centers of Regulatory Excellence for sustainable engagement
- Established liaisons with international harmonization initiatives and organizations, including ICH, IPRP, WHO and others to leverage work

Convergence

APEC RHSC (2)

apec.org/rhsc

Regulatory Harmonization Steering Committee

APEC

Life Sciences Innovation Forum

Advanced Therapies Priority Work Area:

- Regulatory “co-champions” – Singapore HSA and US FDA; BIO sub-champion; ARM industry coalition coordinator
- Strategic Roadmap document to guide effort; scope:
  - Cell therapy products
  - Stem cell based products
  - Gene therapy products (including gene modified cells, iPSCs)
  - Tissue engineered products
  - Xeno-based products – products containing viable animal cells

    Note: non-viable human tissues are regulated differently in different jurisdictions → tissues, transplant products or medicinal products; non-viable animal cells/tissues are excluded because regulated as medical devices
- Duke-National University of Singapore, Northeastern University, and USP designated CoEs for Advanced Therapies
- Draft Core Curriculum in development

Convergence

WHO

2018 ICDRA Meeting

- Member States noted potential impact of ATMPs for global public health
- Highlighted need, especially in LMICs, to build scientific knowledge and strengthen regulatory capacity to provide oversight of these products
- Areas identified as priorities:
  - Define what products constitute ATMPs
  - Develop regulatory frameworks for ATMPs based on sound science and risk-based principles
  - Need for global convergence on standards for cell and gene therapy product manufacturing

Convergence

WHO

WHO White Paper on ATMPs (work-in-progress)

- Cover fundamental principles related to regulation of ATMPs
- Intended to provide a roadmap of considerations so LMICs can devise a regulatory system for oversight of cell and gene therapies tailored to the country's health system strategy and resources
- Build on benefit-risk framework
- Integrate concept of 'reliance' to leverage work of trusted NRAs
- Goal is to establish a regulatory framework in LMICs to ensure access to ATMPs of assured quality, safety, and efficacy (protect patients from exploitation)

International Council for Harmonisation

ich.org

Harmonization

- First gene therapy guideline taken up; endorsed June 2019
- S12: Non-clinical Biodistribution Studies for Gene Therapy Products
- Topic proposal based on IPRP Reflection Paper of same topic
- Goal to provide recommendations on the elements of nonclinical studies performed, to include Biodistribution assessment; to contribute to the streamlined development of the Gene Therapy products, while maintaining scientific rigor and minimizing the use of animals
- Rapporteur: MHLW/PMDA Japan; Regulatory Chair: US FDA

Summation

- Synergy sought between all the venues discussed - All these individual efforts strive to connect to the greater body of effort
- Given the range of products in this category, the state of the science, and the diverse maturity levels in their regulation globally, various approaches are underway to advance harmonization in the broadest sense of the word. No single effort can address all the needs
- The level of attention and energy devoted to these efforts are testimony to the shared view of the promise for better human health that these products hold