Setting the Scene

The ATMP Regulatory Environment

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ICMRA

International Coalition of Medicines Regulatory Authorities

Alliance for Regenerative Medicine

International membership organization

- Dedicated to realizing the promise of safe and effective regenerative medicines for patients around the world
- Cell and gene therapy, tissue engineering

350+ members

- Small and large companies, non-profit research institutions, patient organizations, and other sector stakeholders
- Across 25 countries

Priorities:

- Clear, predictable, and harmonized **regulatory** pathways
- Enabling market access and value-based **reimbursement** policies
- Addressing industrialization and **manufacturing** hurdles
- Conducting key stakeholder outreach, **communication**, and education
- Facilitating sustainable access to **capital**

Sector Overview

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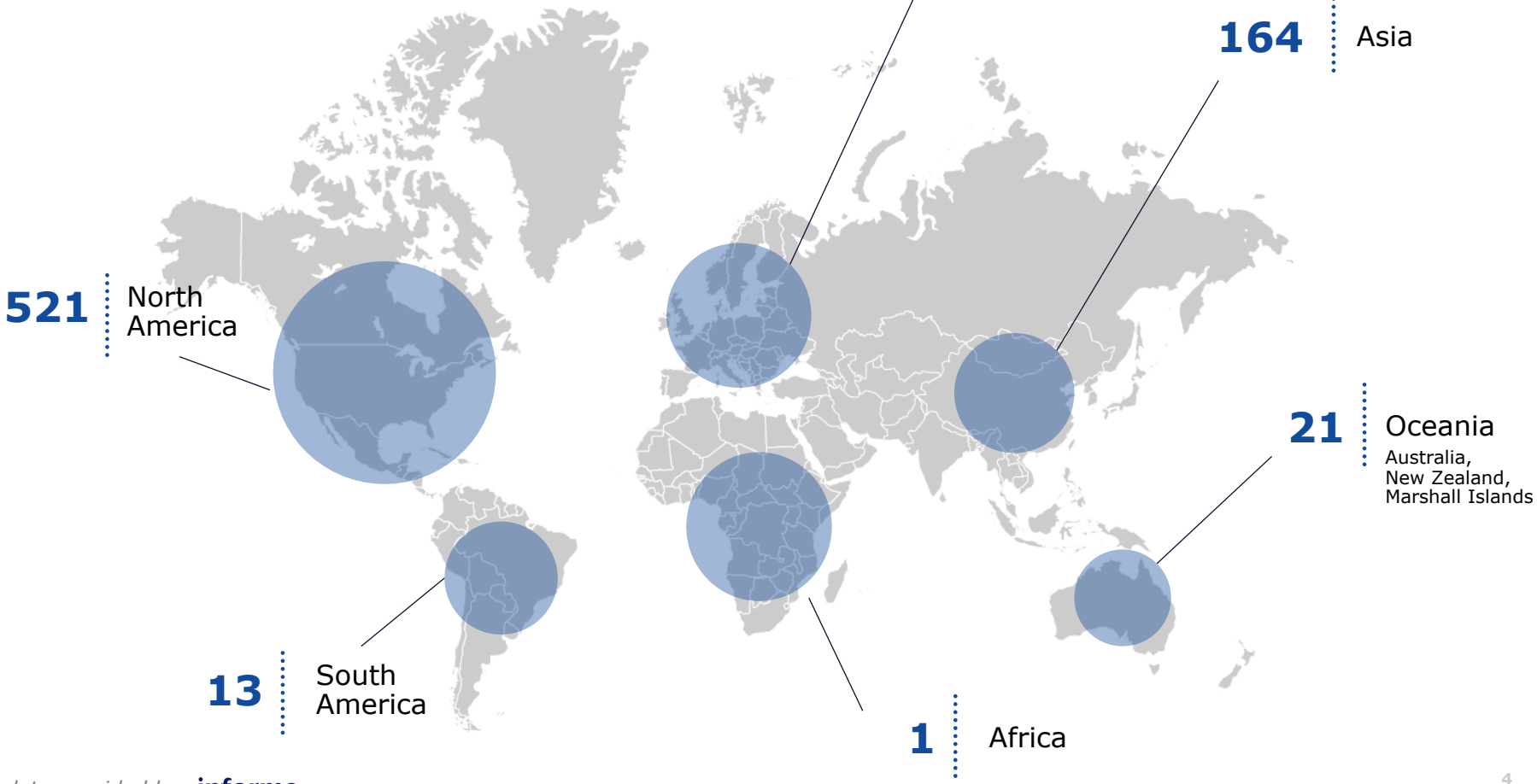
Current Global Sector Landscape

953+
ATMP Developers Worldwide, Including Gene and Cell Therapies and Tissue Engineering



Source data provided by: informa

Patient Impact of Recently Approved Products

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Therapy Name	Product Developer	Response
Kymriah	Novartis	• **40%** of patients with R/R DLBCL treated experienced a complete response • **82%** of patients with R/R B-Cell ALL treated experienced complete remission or complete remission with incomplete hematologic recovery
Yescarta	Kite Pharma, a Gilead company	• **58%** of patients with R/R B-Cell NHL treated experienced a complete response
LUXTURNA	Spark Therapeutics	• **55%** of patients treated showed an improvement of 2+ light levels darker after treatment
Zolgensma	AveXis / Novartis	• **93%** of patients SMA Type 1 treated were alive without permanent ventilation at 24 months post-treatment
Zynteglo	bluebird bio	• **75%** of patients with TDT without β0/β0 genotype treated achieved transfusion independence

ATMP Clinical Trials by Phase and Technology Type

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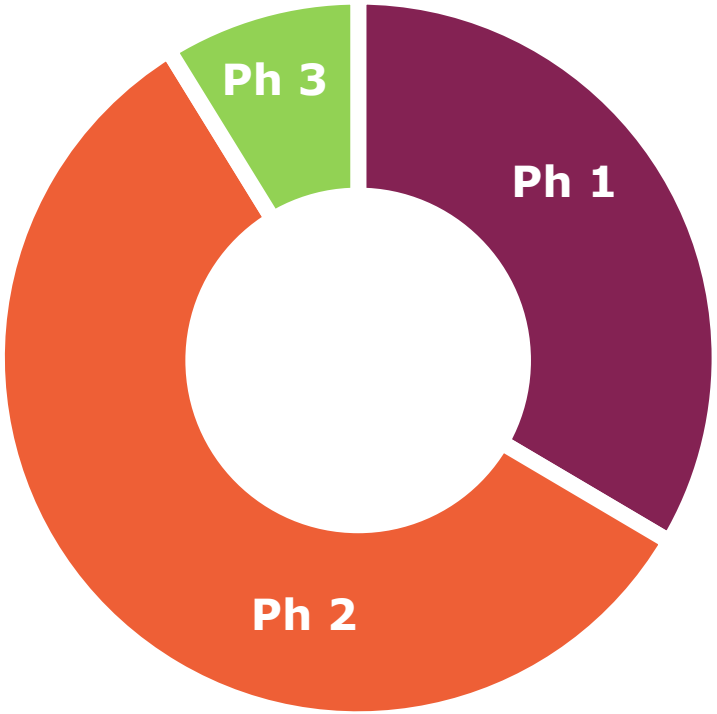
1,071 total ongoing ATMP clinical trials worldwide



Phase 1: 366
across all tech types
and indications

Gene Therapy: 117
Gene-Modified Cell Therapy: 199
Cell Therapy: 44
Tissue Engineering: 6

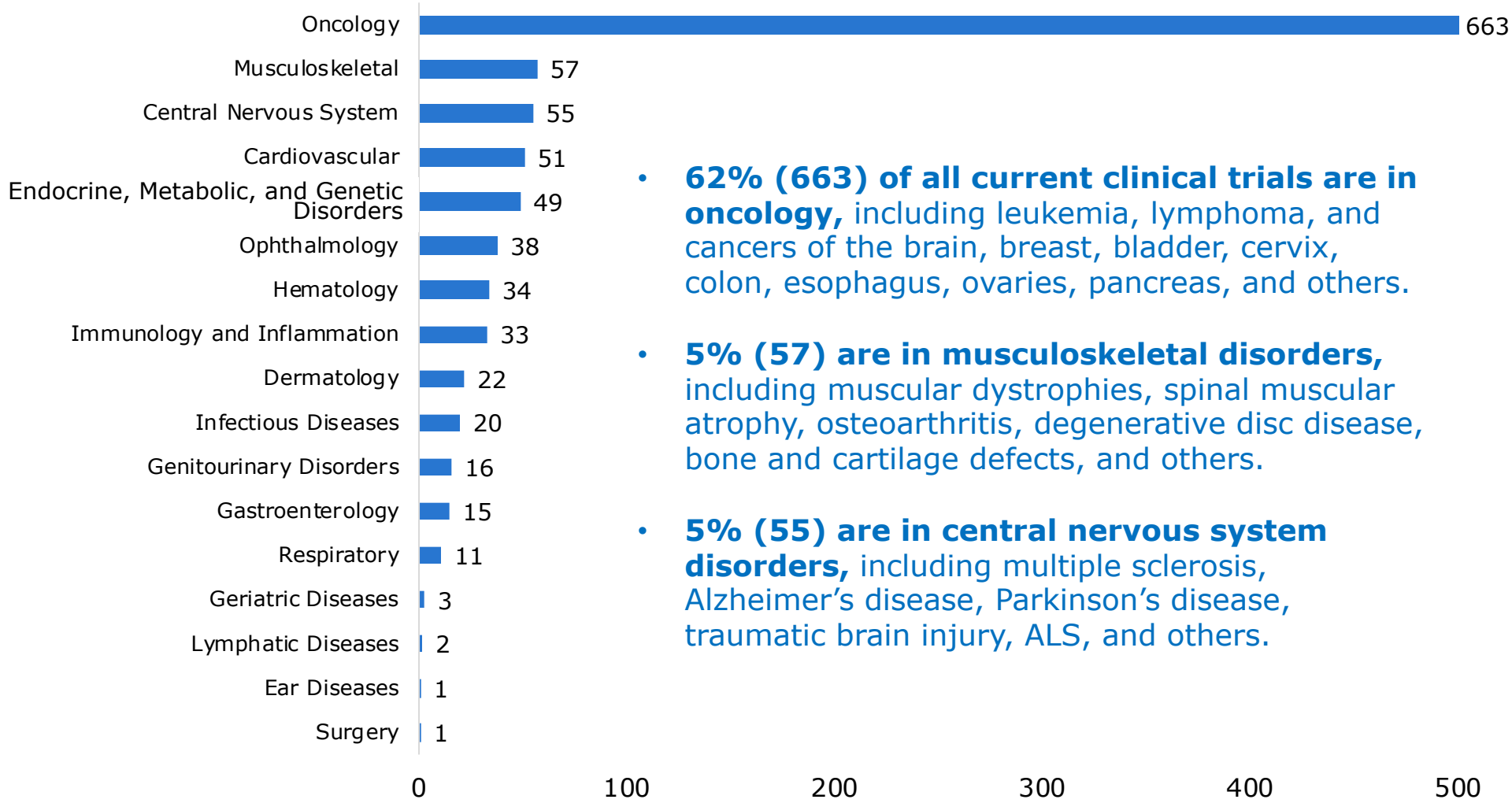
Phase 2: 609
across all tech types
and indications

Gene Therapy: 227
Gene-Modified Cell Therapy: 205
Cell Therapy: 154
Tissue Engineering: 23

Phase 3: 96
across all tech types
and indications

Gene Therapy: 32
Gene-Modified Cell Therapy: 16
Cell Therapy: 31
Tissue Engineering: 17

ATMP Clinical Trials by Therapeutic Area



- **62% (663) of all current clinical trials are in oncology,** including leukemia, lymphoma, and cancers of the brain, breast, bladder, cervix, colon, esophagus, ovaries, pancreas, and others.
- **5% (57) are in musculoskeletal disorders,** including muscular dystrophies, spinal muscular atrophy, osteoarthritis, degenerative disc disease, bone and cartilage defects, and others.
- **5% (55) are in central nervous system disorders,** including multiple sclerosis, Alzheimer's disease, Parkinson's disease, traumatic brain injury, ALS, and others.

MIT NEWDIGS Analysis

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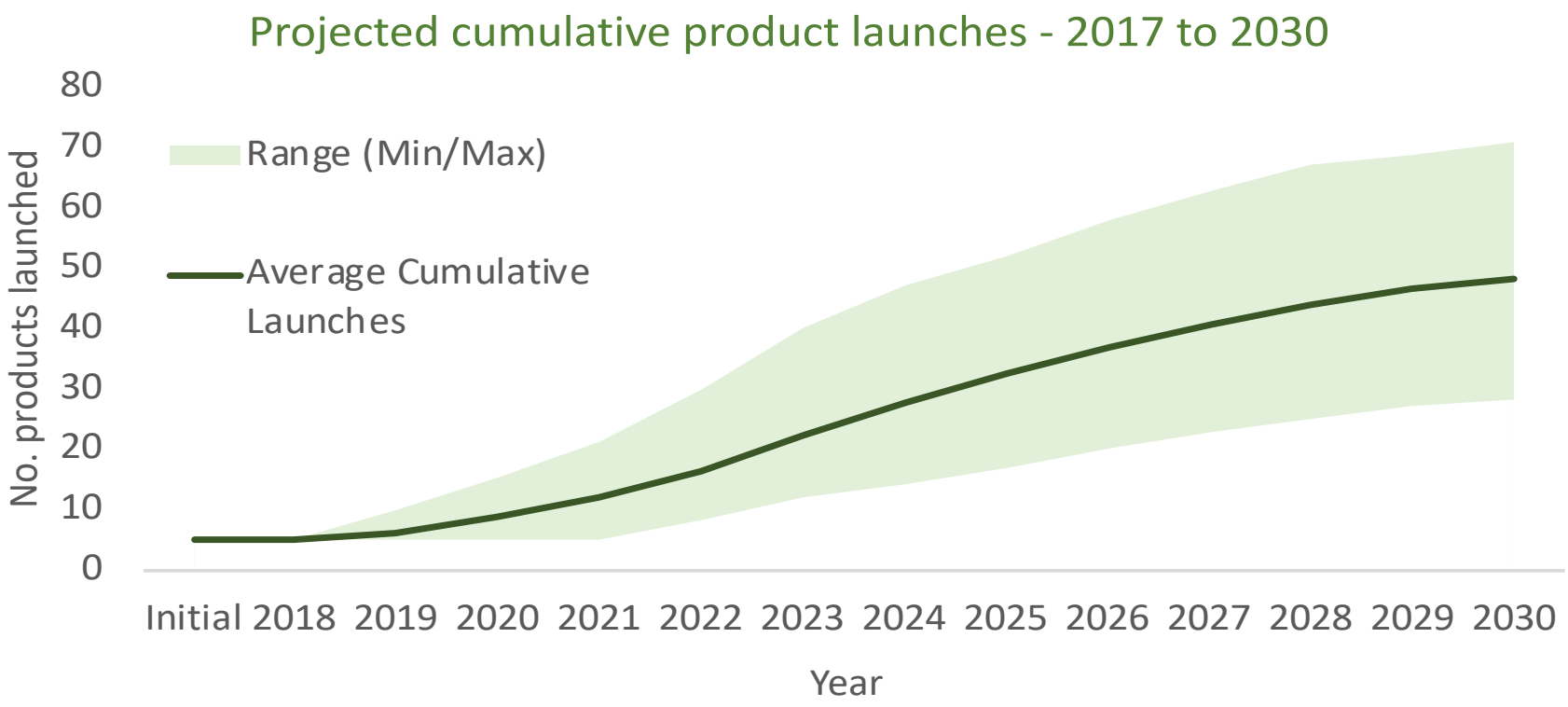
MIT's NEWDIGS initiative projects that there will be **40-60 product launches** and **500,000+ patients treated** with ATMPs by **2030**



Select Anticipated Near-Term Approvals (Global)

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Gene Therapy

Zolgensma (AveXis / Novartis)
- Spinal muscular atrophy type 1
- Decision expected: early 2020 EU and Japan

GT-AADC (PTC Therapeutics)
- AADC deficiency
- Expects to file: late 2019 (US)

Zynteglo (bluebird bio)
- Beta thalassemia
- Expects to file: 2019 (US)

Valrox (BioMarin)
- Hemophilia A
- Expects to file: Q4 2019 (US & EU)

GS010 (GenSight Biologics)
- Leber hereditary optic neuropathy
- Expects to file: H2 2020 (US & EU)

AT132 (Audentes Therapeutics)
- X-linked myotubular myopathy
- Expects to file: H2 2020 (US)

OTL-101 (Orchard Therapeutics)
- ADA-SCID
- Expects to file: 2020 (US)

OTL-200 (Orchard Therapeutics)
- Metachromatic leukodystrophy
- Expects to file: 2020 (US & EU)

Select Anticipated Near-Term Approvals (Global)

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Cell-Based Immuno-Oncology

Rivo-cel (Bellicum Pharmaceuticals)
- HSCT to treat blood cancers
- Expects to file: EOY 2019 (EU)

tab-cel (Atara Biotherapies)
- EBV-PTLD
- Expects to file: 2H 2019 (US)

liso-cel (Celgene)
- Diffuse large B-cell lymphoma (DLBCL)
- Expects to file: Q4 2019 (US)

ide-cel (bluebird bio / Celgene)
- Multiple myeloma
- Expects to file: 1H 2020 (US)

P-BCMA-101 (Poseida Therapeutics)
- Multiple myeloma
- Expects to file: 2020 (US)

Lifileucel (Iovance)
- Advanced metastatic melanoma
- Expects to file: 2020 (US)

LN-145 (Iovance)
- Advanced metastatic cervical cancer
- Expects to file: 2H 2020 (US)

Select Anticipated Near-Term Approvals (Global)

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Cell Therapy

SB623 (SanBio)
- Traumatic brain injury
- Expects to file: January 2020 (Japan)

Remestemcel-L (Mesoblast)
- Acute graft versus host disease
- Decision expected: 2020 (US)

TEMCELL (Mesoblast / JCR Pharma)
- Epidermolysis bullosa
- Decision expected: 2020 (Japan)

Tissue-Based

RVT-802 (Enzyvant Therapeutics)
- Complete DiGeorge anomaly
- Decision expected: 2019 (US)

Humacyl (Humacyte)
- End stage renal disease
- Expects to file: 2020 (US)

Stratagraft (Mallinckrodt)
- Deep partial thickness burns
- Expects to file: 2020 (US)

Market Access Landscape

As of October 2019

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Kymriah

Yescarta

Luxturna

Alofisel

Imlygic

Kymriah

Luxturna

Strimvelis

Yescarta

Holoclar

Imlygic

Kymriah

Strimvelis

Yescarta

Luxturna

Holoclar

Imlygic

Strimvelis

Kymriah

Yescarta

Imlygic

Kymriah

Luxturna

Yescarta

Zolgensma

Kymriah

CADTH Assessment: Would be cost effective if price lowered

Yescarta

Kymriah

Kymriah

Collategene

Positive HTA/Payer Opinion Reimbursed

Zynteglo, which was approved in Europe in June 2019, is currently working with payers in UK, Italy, Germany, France for its initial commercial rollout in 2020.

The ATMP Regulatory Environment

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Why Are ATMPs Different From Traditional Medicines?

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- **Small patient populations:** Many of the cell and gene therapies expected to come to market within the next few years target orphan and ultra-orphan indications with very small patient populations
- **Limited clinical data:** Small patient populations, long lasting effects, and blinding difficulties make traditional large scale trials difficult
- **Manufacturing techniques are evolving:** As the science advances, the sector is rapidly developing new technologies for manufacturing and quality control to meet patient need
- **Source materials:** The individual, and thus high variable, nature of many source materials for cell and gene therapies poses a challenge for traditional measures of quality control
- **Lack of Standards:** There's a lack of standards for many key processes in regenerative medicine, such as potency assays and cell collection
- **Platform technologies:** Many new platforms for the creation and delivery of cell and gene therapies are expected to advance to the clinic within the next 5 years
- **Single dose administration:** Many ATMPs are expected to create a durable, potentially permanent change to a patient's body

Regulatory Best Practices

- ***Resource development:*** We must work together to ensure that there are a sufficient amount of properly trained regulators, product reviewers, and inspectors to manage the growing number of CT/GT applications and products

- ***Pathways for interaction:*** Early and frequent interactions between developers and regulators is a key component of successful expedited review programs, including RMAT and PRIME. Meetings between the sector and regulatory bodies, similar to liaison meetings with the FDA, help to identify challenges for sponsors and the regulator

- ***Patient safety:*** Enforcement of regulations to protect patients from those who are operating outside of regulatory frameworks

Patient Safety

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It is critical to develop, adopt, and enforce science-based regulations that protect patients

- **Many actors operate outside existing regulatory frameworks, putting patients and the sector as a whole at risk**
  - *In the US: hundreds of unregulated clinics as well as physician practices offering "stem cell treatments"*
  - *Ex US: stem cell tourism; gene-edited babies*

- **Some market pathways have been established or proposed that bypass important regulatory protections**
  - In Europe: The Hospital Exemption enables patients to receive an ATMP under controlled conditions in cases where no authorized therapy is available for an indication with a high unmet medical need
  - In the US: A "conditional approval" pathway was proposed but ultimately rejected
  - These efforts could lead to patient harm and provide disincentives for investment in clinical trials/product development
  - ARM's view: ***we need a regulatory framework that ensures products reach patients quickly without lowering regulatory approval standards*** (e.g., RMAT)

Recommendations for Regulators

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Regulatory Convergence

Key areas of focus include GMPs, cell sourcing, and donor testing

CMC Rules & Guidances

Review regulations and guidances and modify as needed to accommodate differences between cell and gene products and other biologics; commit to regular updates

Use of Registry Data

Increased acceptance of registry data in product review, approval, and post-marketing requirements; agree on standards and invest in infrastructure for the collection of RWE

"Sameness" Guidances

Develop guidance on sameness/similarity and related topics that support orphan product development for cell and gene therapies

Looking Beyond the Horizon

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Emerging ATMP Regulatory Issues

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Better coordination between regulators and payers

- Lack of coordination and different requirements can delay reimbursement and patient access post-approval
- In the US, differing definitions between FDA and CMS of "newness" and "clinical improvement"
- Duplication/differences in post-market data requirements

Emerging ATMP Regulatory Issues

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Regulation of novel platform technologies

- As the science evolves, how do regulators plan to review technologies that underlie multiple cell and gene therapy technologies?
    - *Parent-child INDs, master files*

- Next-gen technologies include: novel capsids; non-viral vectors, synthetic promoters that enable stronger and more specific expression inducible elements to regulate gene expression temporally or in response to external stimuli; molecular kill switches to improve safety; cell cloaking technologies, etc.

Emerging ATMP Regulatory Issues

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Genome Editing

- Existing, robust regulatory frameworks are sufficient for therapies using somatic cell genome editing
- National/Regional regulatory frameworks should establish clear controls on in-human germline genome editing
- The international community needs a “Germline 911” system for reporting unethical and inappropriate research

For More

Visit **www.alliancerm.org** to access additional resources, including:

- Quarterly regenerative medicine sector reports
- Upcoming near-term clinical trial milestones & data readouts
- Access to slides, graphics, and figures from ARM presentations
- Our weekly sector newsletter, a robust round-up of business, clinical, scientific, and policy news in regenerative medicine
- Commentary from experts in the field

Thank You!

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Medicine