MINISTRY OF INDUSTRY AND TRADE OF RUSSIA

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Overcoming Barriers: Practical Solutions for Accelerating ATMP Integration into Healthcare Systems

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A new Paradigm in Medicine

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Gene Therapy

Introduces genetic material to correct or modify cells and treat hereditary or acquired diseases.

Cell Therapy

Uses living cells, manipulated outside the body, to repair, replace, or restore tissue function.

Tissue Engineering

Combines cells, biomaterials, and growth factors to create functional tissues that regenerate damaged organs.

Global Regulatory Labyrinth

US FDA (U.S.)

Approach: Flexible in clinical development, strict in manufacturing (CMC). Accelerated pathways like RMAT and Breakthrough Therapy.

EU EMA (EU)

Approach: Centralized and harmonized approval. Allows "Hospital Exemption" for compassionate use and the PRIME program.

JP PMDA (Japan)

Approach: Pioneer in early conditional approval with preliminary data. Fast-track "Sakigake" for innovative products.

AU TGA (Australia)

Approach: Risk-based system (Classes 1-4). Offers provisional approval and exemptions for autologous products.

Latin America regulatory approaches

CL ISP (Chile)

Approach: Proactive with a new, specific regulatory proposal. Focus on a central authority and conditional approvals to speed up access.

BR ANVISA (Brazil)

Approach: Has a specific framework for "Advanced Therapy Products" with defined pathways for registration and clinical trials, though adoption can be complex.

MX COFEPRIS (Mexico)

Approach: Focuses on a "biotechnology" category with specific requirements for cell and gene therapies, working to streamline a robust review process.

🌎 Regional Harmonization

Approach: The main opportunity lies in regional bodies (e.g., MERCOSUR) to align standards and create a more predictable market for developers.

The 5 Major Barriers to Adoption

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Manufacturing & Logistics

Personalized production and ultra-demanding cold chain are difficult to scale and maintain.

Regulation & Harmonization

Emerging regulatory frameworks and lack of global alignment create uncertainty and delay access.

Quality Control Capabilities

Traditional pharmaceutical labs lack the capacity to analyze the living nature of ATMPs.

Economics & Reimbursement

Million-dollar treatment costs and outdated payment models hinder funding by healthcare systems.

System Readiness

Lack of infrastructure, trained personnel, and high workload to implement these complex therapies.

Regulatory Adaptation & Harmonization

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Specific Regulatory Frameworks

Create regulations that are clear, proportional, and specifically tailored to the unique nature of Advanced Therapy Medicinal Products (ATMPs), such as the Chilean proposal.

Accelerated & Conditional Approval Pathways

Implement mechanisms like the FDA's RMAT, EMA's PRIME, or Japan's Sakigake to allow for early market access based on preliminary data, with robust post-commercialization follow-up and monitoring.

International Regulatory Harmonization

Foster collaboration between global agencies (e.g., ICMRA, WHO) to reduce redundant studies, streamline the approval process, and facilitate access in multiple jurisdictions.

Flexible Clinical Trial Designs

Allow for adaptive study designs and the acceptance of data from smaller patient populations when justified, accelerating the path to clinical evidence.

Detailed Guidance & Transparency

Publish clear technical guidelines for manufacturers and researchers to increase predictability and efficiency, ensuring all stakeholders are aligned with the new regulations.

Strengthening Quality Ecosystem

Leverage Clinical Labs

Formally integrate the capabilities and expertise of clinical laboratories into the ATMP quality control process.

Collaborative Models

Establish strategic alliances between pharmaceutical QC labs and clinical labs to ensure comprehensive evaluation and compliance with GMP standards.

Specific Analytical Assays

Promote research and development of fast and reliable analytical methods for the unique characteristics of ATMPs.

Flexible Manufacturing Standards

Adapt Good Manufacturing Practices (GMPs) for the personalized and small-scale production of ATMPs without compromising safety.

Training & Specialization

Educate and train a new group of professionals in the quality control of advanced biological therapies.

Innovative Reimbursement Models

Outcome-Based Agreements

Payment is tied to the therapy's demonstrated clinical effectiveness over time, ensuring value for money and shared risk.

Milestone Payments

Payments are made in fractions as the patient achieves specific, predefined health milestones or outcomes, ensuring a continuous link to performance.

Risk-Sharing Agreements

Agreements between payers and manufacturers to share the financial risk if the treatment does not prove effective or durable for the patient.

Annuity Payment Models

The total cost is distributed over several years, instead of a single, massive upfront payment, making the therapy more financially manageable.

Specific National Funds

Creation of dedicated budgets or funds specifically for financing high-cost, high-impact therapies, ensuring a clear and stable funding source.

Fundamental Differences

Characteristic	Conventional Pharmaceuticals	Advanced Therapies (ATMPs)
Manufacturing	Standardized, large batches	Personalized, small batches, high complexity
Quality Control	Post-analysis release (Pharma Labs)	Release at risk, requires Clinical Lab capabilities (cells, DNA)
Stability	High, simple storage	Very low, short shelf-life, requires cryopreservation
Logistics	Standard supply chain	"Vein-to-vein", ultra-controlled cold chain
Traceability	By product batch	Critical, from donor to patient

Main S&E and CMC Concerns

Safety Concerns

- **Acute Toxicities:** Rapid onset of severe side effects like Cytokine Release Syndrome (CRS) and neurological toxicities, requiring immediate and specialized medical intervention.
- **Immunogenicity:** The body may recognize viral vectors or other components as foreign, leading to an immune response that could reduce efficacy or cause adverse reactions.
- **Off-target Effects:** Engineered cells or genes may affect unintended targets, leading to unpredictable side effects or damage to healthy tissues.
- **Insertional Mutagenesis:** For therapies using viral vectors, there is a theoretical risk of the gene inserting itself into an unintended location in the patient's DNA, potentially activating cancer-causing genes.
- **Long-Term Effects:** The full range of long-term risks, including the potential for secondary malignancies or chronic conditions, is still being studied.

Chemistry, Manufacturing, and Controls (CMC)

- **Manufacturing Complexity:** ATMPs are often personalized and created in small batches ("vein-to-vein" process), making large-scale production, standardization, and quality control extremely challenging.
- **Product Variability:** The living nature of the product means there can be significant variability from batch to batch, which complicates consistency and requires robust quality assurance protocols.
- **Short Shelf-life:** Many ATMPs have a very short shelf-life, necessitating a highly efficient and well-coordinated logistics chain to ensure the product reaches the patient in viable condition.
- **New Analytical Methods:** Traditional pharmaceutical quality control methods are insufficient. New analytical tools are needed to verify the potency, identity, and purity of a living product.
- **Logistical Hurdles:** The "vein-to-vein" process involves complex, ultra-cold supply chains that must be perfectly executed to avoid product loss, which has significant financial and patient-care implications.

Kymriah: A Landmark in ATMPs

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Key Information

Initial U.S. Approval: 2017

Type: CD19-directed CAR-T cell immunotherapy

Manufacturer: Novartis

Indications

- Pediatric & Young Adult B-cell Acute Lymphoblastic Leukemia (ALL) refractory or in 2nd+ relapse
- Adult Relapsed/Refractory (r/r) Large B-cell Lymphoma
- Adult Relapsed/Refractory (r/r) Follicular Lymphoma

Kymriah: A Landmark in ATMPs

Mechanism: The "Vein-to-Vein" Journey

1. **Leukapheresis:** Patient's T-cells are collected from their blood.
2. **Genetic Modification:** T-cells are sent to a manufacturing facility and genetically engineered using a lentiviral vector to express a Chimeric Antigen Receptor (CAR) that targets CD19 (a protein on cancer cells).
3. **Cell Expansion:** The modified CAR-T cells are multiplied in the lab to reach the required dose.
4. **Infusion:** The personalized CAR-T cell therapy is then infused back into the patient.
5. **Targeted Action:** Once in the body, the CAR-T cells recognize and eliminate CD19-expressing cancer cells.

Key Safety Considerations

- **Cytokine Release Syndrome (CRS):** A severe systemic inflammatory response.
- **Neurological Toxicities:** Can manifest as encephalopathy, delirium, or seizures.
- **Secondary Malignancies:** Risk of developing new cancers, including T-cell malignancies.

Zolgensma: First ATMPs approved in Chile

Key Information

Type: Gene Replacement Therapy

Manufacturer: Novartis Gene Therapies

Global Status:

- **U.S. FDA:** Approved in May 2019 for pediatric patients < 2 years.
- **EU EMA:** Conditional marketing authorization in May 2020.
- **Chile ISP:** Approved in 2022.

Indications

- Pediatric patients less than 2 years of age with Spinal Muscular Atrophy (SMA).

Zolgensma: First ATMPs approved in Chile

Mechanism of Action

1. SMA is caused by a missing or defective **SMN1 gene**, leading to insufficient SMN protein.
2. Zolgensma uses a harmless **adeno-associated virus (AAV9) vector** to deliver a new, functional copy of the SMN1 gene.
3. This single infusion provides the cells with the genetic instructions to produce the SMN protein, restoring nerve function and preventing progressive muscle degeneration.

Key Safety Considerations

- **Serious Liver Injury:** Requires close monitoring of liver function before and after administration.
- **Acute Liver Failure:** Has been reported in some cases.
- **Required Steroid Treatment:** Patients must receive corticosteroids to manage potential liver inflammation.

Elevidys: Controversial & Complex Story

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June 2023: Accelerated Approval

The FDA grants accelerated approval for ambulatory patients aged 4-5, a decision made despite a failed primary endpoint in trials. The CBER Director overrules the advisory committee's negative recommendation, citing unmet medical need.

1

June 2024: Full Approval

In an unprecedented move, the FDA grants full approval for ambulatory patients 4+ years old, even after the confirmatory trial officially failed to meet its primary endpoint. The decision rests on "compelling" secondary data points.

2

March - July 2025: Safety Crisis

Tragedy strikes as patient deaths from acute liver failure are reported in non-ambulatory patients. This triggers a full-blown safety crisis, leading Sarepta to voluntarily halt shipments for this group.

3

July 2025: FDA Intervention

The FDA formally requests a halt to all Elevidys shipments and places related clinical trials on hold, revoking the platform technology designation for the AAVrh74 vector amid growing safety concerns.

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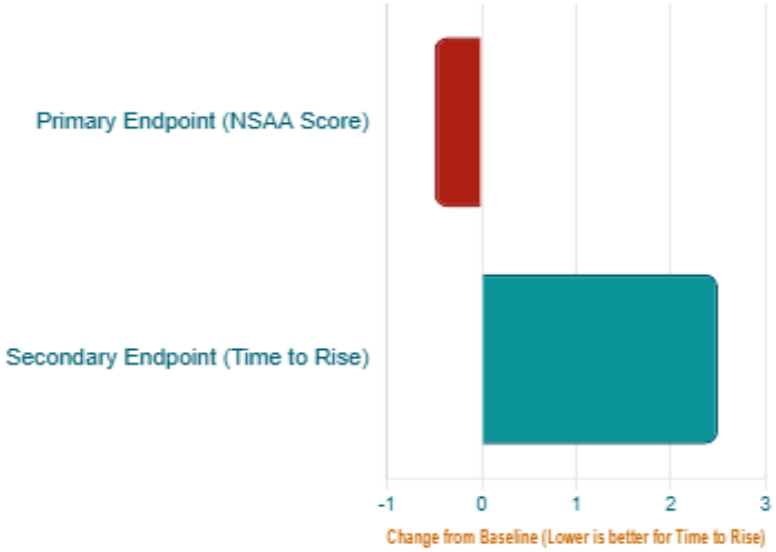
Clinical Trial Paradox

The core of the Elevidys controversy lies in its clinical trial results, which presented a conflicting picture of efficacy that the FDA ultimately interpreted in favor of approval.

Confirmatory Trial Outcome Summary



While the primary goal of improving motor function wasn't met, the FDA pointed to positive results in secondary measures, like the time taken to stand, as evidence of clinical benefit, justifying the approval.

Elevidys: Controversial & Complex Story

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Patient Deaths

Linked to AAVrh74 Vector

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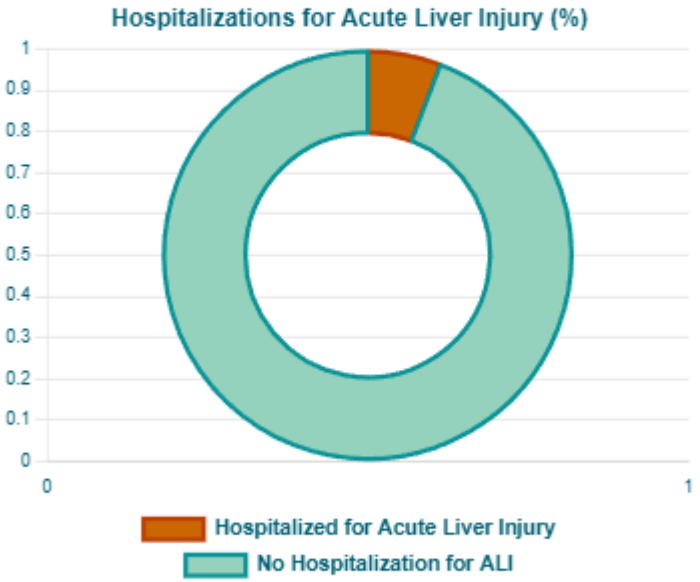
Acute Liver Failure

Identified Cause



Data shows a small but significant percentage of patients experienced hospitalization due to acute liver injury, highlighting the critical need for careful patient selection and post-infusion monitoring.

Regulatory Response & Current Status

In response to the safety crisis, the FDA's actions led to a bifurcated status for Elevidys, creating two distinct paths for different patient populations while risk mitigation strategies are evaluated.

✅

Ambulatory Patients

Shipments Resumed

After an investigation found one patient death to be unrelated, the FDA lifted the hold for walking patients, restoring access for this group.

⏳

Non-Ambulatory Patients

Voluntary Hold Remains

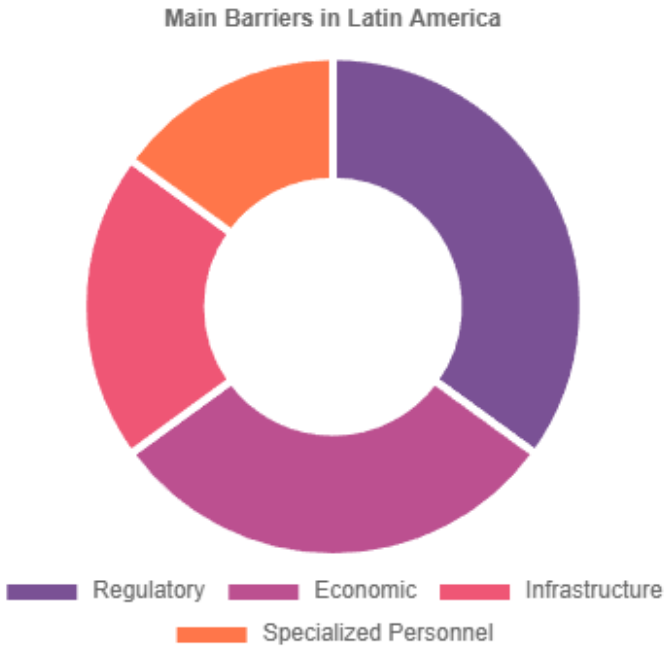
Shipments remain paused for non-walking patients. The FDA and Sarepta are discussing enhanced safety protocols and risk mitigation.

Focus on Latin America

Focus on Latin America: Challenges & Opportunities

Key Regional Barriers

The region faces significant challenges, including limited access to infrastructure, scarcity of specialized personnel, and still-developing regulatory frameworks. Limited economic resources exacerbate the difficulty in funding these therapies.



Case Study: Chile's Regulatory Proposal

The Regulation proposed by Chile's Public Health Institute (ISP) is an example of a proactive effort to create an ecosystem ready for ATMPs.

- ✓ Establishes ISP as the **sole and centralized authority.**
- ✓ Creates an **"Advanced Therapy Evaluation Commission"** to ensure technical expertise.
- ✓ Defines clear conditions for **registration, production, import, and clinical trials.**
- ✓ Focuses on **complete traceability and requires a robust Risk Management Plan.**

Chilean ATMPs regulatory proposal

Centralized Governance & Lifecycle Scope

The proposal establishes the Public Health Institute (ISP) as the sole authority, overseeing the entire lifecycle of an Advanced Therapy Medicinal Product (ATMP) to ensure consistency and efficiency.

Chilean ATMPs regulatory proposal

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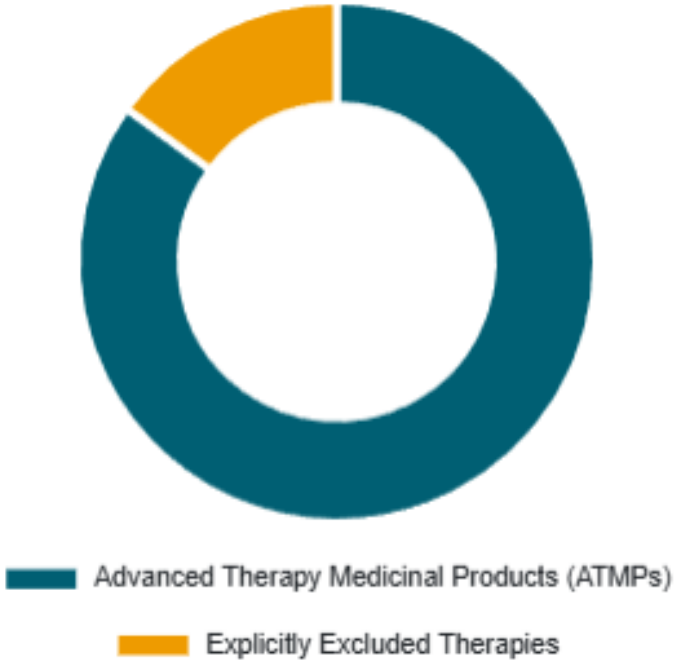
Core Regulatory Principles

The framework is built on interconnected principles that ensure every product meets the highest standards from donor to patient.

Regulatory Scope: In & Out

To prevent overlap and provide clarity, the regulation precisely defines its focus, explicitly excluding certain therapies to concentrate on ATMPs.



Chilean ATMPs regulatory proposal

Implementation & Approval Pathway

A structured, phased implementation provides clear timelines for compliance and establishes modern pathways for market authorization, balancing speed with safety.

Regulation Published

The official starting point for the new regulatory framework.

Within 90 Days

The ISP will issue detailed technical guidelines to support industry compliance.

Conditional Authorizations Begin

A new pathway opens, allowing faster provisional access to critical therapies, followed by verification.

12-Month Transition Period Ends

All new ATMP registrations must fully comply with the new, comprehensive requirements.

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Ministerio de Salud
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