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REGULATORY CONSIDERATIONS FOR ADVANCED THERAPY MEDICINAL PRODUCTS (ATMPS): GLOBAL PERSPECTIVES

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ABSTRACT

Advanced Therapy Medicinal Products (ATMPs), including gene therapy medicinal products, somatic cell therapy medicinal products, tissue-engineered products, and certain combined advanced therapies, represent a major transformation in modern medicine. Unlike conventional small-molecule medicines, ATMPs frequently involve living cells, genetic material, engineered tissues, or combinations of biological and device components, creating distinctive challenges for product characterization, manufacturing, quality control, clinical development, regulatory assessment, and long-term safety monitoring. Regulatory authorities worldwide have therefore developed specialized frameworks to address the unique benefit–risk characteristics of these products. The European Union has established a dedicated ATMP framework under Regulation (EC) No. 1394/2007, with centralized authorization and scientific assessment involving the European Medicines Agency and its Committee for Advanced Therapies. In the United States, cellular and gene therapy products are primarily regulated by the U.S. Food and Drug Administration through the Center for Biologics Evaluation and Research. Japan has adopted a distinctive regulatory pathway for regenerative medical products that includes conditional and time-limited approval. Other jurisdictions, including India, have progressively developed regulatory guidance for cell- and gene-based therapies. Across regions, major regulatory considerations include product classification, chemistry, manufacturing and controls, potency, preclinical evaluation, clinical trial design, manufacturing consistency, traceability, pharmacovigilance, long-term follow-up, and management of post-approval changes. Despite substantial progress, differences in terminology, classification, evidence requirements, manufacturing standards, and approval pathways continue to complicate global development. International regulatory convergence and science-based harmonization will be essential for improving patient access while maintaining product quality, safety, and efficacy.

KEYWORDS: Advanced Therapy, Medicinal Products, ATMPs, FDA, Regulatory Affairs.

1. INTRODUCTION

The development of advanced biological therapies has transformed the pharmaceutical and healthcare landscape. Conventional medicines generally consist of well-characterized chemical entities or biologically derived molecules whose composition, manufacturing processes, pharmacokinetic properties, and mechanisms of action can be relatively well defined. In contrast, advanced therapies may contain living cells, genetically modified cells, viral or non-viral vectors, engineered tissues, or combinations of biological and medical device components.[1]

These products create a distinctive regulatory challenge because the final therapeutic product may be highly dependent on the manufacturing process. Small changes in starting materials, cell culture conditions, genetic modification, purification, formulation, storage, or administration may potentially affect the biological characteristics and clinical performance of the product.

The European Union formally established a dedicated regulatory framework for ATMPs through Regulation (EC) No. 1394/2007. The framework covers gene therapy medicinal products, somatic cell therapy medicinal products, tissue-engineered products, and combined ATMPs. The European Medicines Agency (EMA) provides centralized scientific assessment and authorization for ATMPs.[2]

In the United States, cellular and gene therapy products are primarily regulated by the U.S. Food and Drug Administration (FDA), particularly through the Center for Biologics Evaluation and Research (CBER). FDA has developed a growing body of guidance addressing product development, manufacturing, potency, genome editing, clinical trials, long-term follow-up, and other aspects of cellular and gene therapy development.[3]

Japan has adopted a distinctive framework for regenerative medical products, including a conditional and time-limited approval pathway intended to facilitate earlier access to innovative therapies while requiring subsequent evidence generation. PMDA currently provides specific guidance concerning conditional and time-limited approval and post-approval evaluation.

The rapid emergence of these therapies has therefore made regulatory science an essential component of ATMP development. This review discusses the major regulatory considerations for ATMPs and compares regulatory approaches across major global jurisdictions.[4]

2. Classification of Advanced Therapy Medicinal Products

Correct classification is one of the first regulatory decisions in ATMP development because the classification determines the applicable legislation, regulatory authority, quality requirements, clinical pathway, and marketing authorization procedure.

2.1 Gene Therapy Medicinal Products

Gene therapy products are designed to modify, replace, regulate, or introduce genetic material to achieve a therapeutic effect. These products may involve viral vectors such as adeno-associated virus, adenoviral vectors, lentiviral vectors, or other delivery systems.

2.2 Somatic Cell Therapy Products

Somatic cell therapies involve the administration of manipulated or unmanipulated human cells for therapeutic purposes.[5]

2.3 Tissue-Engineered Products

Tissue-engineered products contain cells or tissues that are engineered or modified to regenerate, repair, or replace human tissue.

2.4 Combined ATMPs

Some advanced therapies contain a medicinal component together with a medical device or structural component.

Examples may include:

- Cells incorporated into a scaffold
- Tissue-engineered products containing medical devices
- Gene-modified cells combined with specialized delivery systems

Such products may require coordinated assessment of both the medicinal and device-related components.

3. Regulatory Challenges Associated with ATMPs

ATMPs present several challenges that differ substantially from those encountered with conventional pharmaceuticals.[6]

3.1 Product Complexity

Many ATMPs are heterogeneous biological systems rather than single molecular entities. The characteristics of the final product may depend strongly on the manufacturing process.[7]

Consequently:

Process → Product characteristics → Biological activity → Clinical performance

This relationship makes process control particularly important.

3.2 Limited Product Characterization

Complete molecular characterization may not always be possible for living cellular products.

3.3 Manufacturing Variability

Manufacturing variability can occur due to:

- Donor variability
- Starting material variability
- Cell expansion
- Culture conditions

For autologous products, the starting material is obtained from the individual patient, creating additional logistical and manufacturing challenges.[8]

4. Chemistry, Manufacturing and Controls (CMC)

CMC requirements represent one of the most critical regulatory components of ATMP development.[9]

The CMC package should demonstrate that the manufacturing process consistently produces a product with appropriate:

- Identity
- Strength
- Quality
- Purity
- Potency
- Safety

For cellular and gene therapies, regulatory authorities recognize that conventional pharmaceutical manufacturing approaches may not always be directly applicable.[10]

The FDA issued specific 2026 guidance describing flexibility in CMC requirements for human cellular and gene therapy products submitted in support of biologics license applications.

Table 1: Important CMC components.

CMC component	Major consideration
Starting materials	Source, qualification and traceability
Cell banks	Identity, sterility and stability
Viral vectors	Identity, potency, purity and safety
Manufacturing process	Controlled and reproducible process
Analytical methods	Validated or appropriately qualified methods
Potency	Relevant biological activity
Sterility	Microbial contamination control
Stability	Shelf-life and storage conditions
Packaging	Compatibility and integrity
Transportation	Temperature and chain-of-custody control

5. Good Manufacturing Practice Requirements

GMP is fundamental to ensuring that ATMPs are manufactured consistently and safely.[11]

ATMP-specific GMP considerations include:

- Controlled manufacturing environments
- Prevention of microbial contamination
- Appropriate environmental monitoring
- Qualified equipment
- Validated critical processes
- Personnel training
- Batch documentation
- Traceability
- Chain of identity
- Chain of custody
- Deviation management

- Change control
- Quality risk management

The European Commission has established GMP guidelines specifically adapted to the characteristics of ATMP manufacturing.[12]

For patient-specific therapies, chain-of-identity and chain-of-custody systems become particularly important because mixing patient-derived materials can have severe consequences.

6. Quality Control and Potency

Potency testing is one of the most challenging aspects of ATMP regulation.

For conventional medicines, potency may often be associated with a defined chemical concentration. For ATMPs, however, therapeutic activity may depend on complex biological functions.[13]

Potential potency assays include:

- Functional cellular assays
- Cytotoxicity assays
- Cytokine-release assays
- Gene-expression assays
- Receptor-binding assays
- Differentiation assays
- Biological activity assays

A suitable potency strategy should establish a scientifically meaningful relationship between the measured biological activity and the intended mechanism of action.[14]

The FDA's cellular and gene therapy guidance framework includes specific regulatory considerations related to potency and product quality.

7. Preclinical Regulatory Requirements

Before clinical administration, ATMP developers must generate appropriate non-clinical evidence.

Major areas include:

Pharmacology

- Mechanism of action
- Biological activity
- Target engagement
- Dose-response relationship

Safety pharmacology

Assessment may be necessary to identify potential effects on:

- Cardiovascular system
- Respiratory system
- Central nervous system

Toxicology

Depending on the product, studies may investigate:

- Acute toxicity
- Repeat-dose toxicity
- Immunotoxicity
- Tumorigenicity
- Genotoxicity
- Biodistribution
- Persistence
- Shedding

For gene therapies, special attention may be given to vector biodistribution, persistence, immune responses, and potential unintended genomic effects.[15]

8. Clinical Trial Considerations

Clinical development of ATMPs requires carefully designed studies because conventional randomized controlled trial models may not always be practical for rare diseases or highly individualized therapies.

Important considerations include:

- Patient population
- Dose selection
- Route of administration
- Treatment schedule
- Control group
- Clinical endpoints
- Biomarkers
- Immunogenicity
- Long-term follow-up
- Manufacturing consistency

The FDA has specifically issued guidance concerning innovative clinical-trial designs for cellular and gene therapy products intended for small populations.

For rare diseases, regulators may permit innovative approaches when justified by disease characteristics and available scientific evidence.[16]

9. European Union Regulatory Framework

The EU has one of the most structured regulatory systems specifically designed for ATMPs.

Regulation (EC) No. 1394/2007 provides the central legislative framework. The Committee for Advanced Therapies (CAT) plays a specialized role in evaluating the quality, safety, and efficacy of ATMPs.

Major EU regulatory components

1. ATMP classification
2. Scientific advice
3. Clinical trial authorization
4. GMP compliance
5. Centralized marketing authorization
6. Risk-management planning
7. Pharmacovigilance
8. Long-term safety monitoring

All ATMPs in the EU are authorized centrally through the EMA's centralized procedure.

EMA also provides an optional ATMP classification procedure to help developers resolve borderline classification questions. The Committee for Advanced Therapies provides a scientific recommendation on classification.[17]

10. United States Regulatory Framework

In the United States, cellular and gene therapy products are primarily regulated by the FDA through CBER.

The regulatory framework includes:

- Investigational New Drug application (IND)
- Chemistry, Manufacturing and Controls
- Preclinical studies
- Clinical trials
- Biologics License Application (BLA)
- Post-marketing surveillance
- Long-term follow-up

FDA has established numerous guidance documents covering cellular and gene therapy development, including genome editing, CAR-T products, manufacturing changes, long-term follow-up, potency, and CMC considerations.[18]

The FDA's regulatory approach emphasizes product-specific risk assessment while allowing flexibility where scientifically justified.

11. Japan Regulatory Framework

Japan has developed a distinctive framework for regenerative medical products.

The Pharmaceuticals and Medical Devices Agency (PMDA) provides regulatory review and scientific guidance for regenerative medical products.

One of the most notable features is the conditional and time-limited approval pathway.

This mechanism can facilitate earlier availability of regenerative medical products when preliminary evidence supports efficacy and safety, while additional clinical evidence is generated after approval.[19]

PMDA currently provides guidance concerning conditional and time-limited approval and subsequent efficacy evaluation.

Japan's framework therefore represents a regulatory model that attempts to balance:
Early patient access + continued evidence generation + regulatory oversight

12. Regulatory Perspective in India

India is increasingly developing its regulatory infrastructure for advanced biological and regenerative therapies.
Regulatory oversight involves authorities including:

- Central Drugs Standard Control Organization (CDSCO)
- Drugs Controller General of India (DCGI)
- Department of Biotechnology (DBT)
- Institutional Ethics Committees
- Review committees relevant to recombinant DNA and biological research

Indian developers may encounter regulatory requirements involving:

- Product classification
- Preclinical evaluation
- Manufacturing controls
- Clinical trial authorization
- GMP
- Quality control
- Ethical approval
- Pharmacovigilance
- Long-term monitoring

For gene and cell-based products, coordination between regulatory, ethical, biosafety, and scientific authorities is particularly important.

India's regulatory system continues to evolve alongside the rapid development of cell and gene therapy technologies.

13. Comparison

Table 2: Global Regulatory Frameworks.

Parameter	European Union	United States	Japan	India
Regulatory authority	EMA	FDA	PMDA/MHLW	CDSCO/DBT and related authorities
Major terminology	ATMP	Cellular & Gene Therapy Products	Regenerative Medical Products	Cell/Gene/Regenerative therapies
Central feature	Dedicated ATMP framework	Risk-based biologics framework	Conditional/time-limited pathway	Developing regulatory framework
Classification	Formal ATMP classification	Product-specific determination	Regenerative medical product classification	Product-specific regulatory assessment
Marketing authorization	Centralized	BLA	MHLW approval	CDSCO approval
GMP	ATMP-specific	CGT-specific	GMP requirements for	GMP and applicable

	GMP	requirements	regenerative products	biological-product requirements
Post-market monitoring	Pharmacovigilance and risk management	Post-marketing surveillance and long-term follow-up	Use-results surveys/re-examination	Pharmacovigilance and regulatory monitoring
Special pathway	Advanced therapy incentives	RMAT and other expedited programs	Conditional/time-limited approval	Expedited pathways may apply depending on product

14. Pharmacovigilance and Long-Term Follow-Up

Long-term safety monitoring is particularly important for ATMPs because some adverse events may occur years after treatment.[20]

Potential long-term risks include:

- Delayed immune reactions
- Tumorigenicity
- Insertional mutagenesis
- Off-target genomic effects
- Persistent vector-related effects
- Abnormal cell proliferation
- Unexpected tissue distribution

Therefore, pharmacovigilance programs may require:

- Long-term patient follow-up
- Patient registries
- Periodic safety reporting
- Adverse-event monitoring
- Product traceability
- Risk-management plans

The FDA maintains specific guidance concerning long-term follow-up after administration of certain human gene therapy products.

The EMA also emphasizes continued monitoring of ATMP safety and efficacy following authorization.

15. Traceability and Chain of Identity

Traceability is particularly important for cell-based and personalized therapies.

For autologous products, the patient's cells may undergo several stages:

Patient → Collection → Manufacturing → Testing → Storage → Transportation → Administration

At every stage, the product must remain correctly associated with the intended patient.

Important documentation includes:

- Patient identification
- Collection records
- Manufacturing records
- Batch information

- Testing results
- Storage records
- Transportation records
- Administration records

Digital tracking technologies can improve traceability and reduce the risk of identity errors.

16. Post-Approval Changes and Comparability

Manufacturing processes for ATMPs frequently evolve during clinical development and commercial manufacturing.[21]

Changes may involve:

- Manufacturing site
- Raw materials
- Cell culture conditions
- Vector production
- Equipment
- Analytical methods
- Formulation
- Storage
- Scale

Regulators therefore require scientifically justified comparability assessments.

The fundamental question is:

Does the manufacturing change alter the quality, safety, or efficacy of the product?

For ATMPs, this question can be particularly difficult because relatively small process changes may potentially affect biological characteristics.

Japan, for example, provides specific regulatory mechanisms concerning post-approval change management for regenerative medical products.

17. Regulatory Incentives for ATMP Development

Because ATMP development is technically complex and often targets rare or serious diseases, regulators have established various mechanisms to support development.[22]

These may include:

- Scientific advice
- Early regulatory interaction
- Priority review
- Accelerated approval pathways
- Orphan-drug incentives
- Conditional authorization
- Breakthrough or regenerative medicine designations
- Support for small and medium-sized enterprises

The EU framework includes specific incentives for SMEs developing ATMPs.

Such mechanisms can reduce development uncertainty and facilitate communication between developers and regulatory authorities.

18. Major Regulatory Challenges[23]

Despite significant progress, several challenges remain.

18.1 Lack of Global Harmonization

Different jurisdictions use different:

- Definitions
- Classification systems
- Approval pathways
- Clinical requirements
- Manufacturing standards
- Long-term monitoring requirements

CONCLUSION

Advanced Therapy Medicinal Products represent one of the most significant developments in modern pharmaceutical science, but their complex biological nature creates regulatory challenges that differ substantially from those associated with conventional medicines. Effective regulation requires integrated assessment of product quality, manufacturing processes, non-clinical safety, clinical efficacy, long-term risks, and post-market performance.

The European Union has established a dedicated ATMP framework with centralized authorization through EMA, while the United States regulates cellular and gene therapy products primarily through the FDA's biologics framework. Japan has developed a distinctive conditional and time-limited approval model for regenerative medical products, whereas India continues to strengthen its regulatory infrastructure for advanced biological therapies.

Despite differences between jurisdictions, common regulatory priorities are emerging, particularly around GMP, potency, traceability, manufacturing consistency, clinical evidence, long-term safety, and risk-based regulation. Continued international cooperation and harmonization will be essential to reduce regulatory duplication, facilitate global development, and improve timely patient access.

Ultimately, the future of ATMP regulation will depend on maintaining a balance between innovation, scientific rigor, patient safety, manufacturing quality, and timely access to transformative therapies.

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