IJBPAS, September, 2024, 13(9): 4630-4640

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

HARMONIZATION OF ATMP REGULATIONS ACROSS EU MEMBER STATES: IMPACT ON APPROVAL TIMELINES AND PROCESSES

TAMIL SR AND RAJU KAMARAJ R*

Department of Pharmaceutical Regulatory Affairs, SRM College of Pharmacy, SRM Institute of Science and Technology, Kattankulathur- 603203, Chengalpattu, Tamil Nadu, India

***Corresponding Author: Dr. Raju Kamaraj: E Mail: kamarajr@srmist.edu.in**

Received 18th July 2023; Revised 20th Sept. 2023; Accepted 10th Dec. 2023; Available online 1st Sept. 2024

https://doi.org/10.31032/IJBPAS/2024/13.9.8342

ABSTRACT

Advanced therapy medicinal products (ATMPs) are a rapidly developing class of innovative therapies that use living cells, tissues, or genes to treat or prevent diseases. The EU has a specific regulatory framework for ATMPs, which is designed to ensure the safety and efficacy of these products while also facilitating their development and access to patients. The EU ATMP regulation (Regulation (EC) No 1394/2007) establishes a multidisciplinary Committee for Advanced Therapies (CAT) to assess the quality, safety, and efficacy of ATMPs. The EU ATMP regulation also provides for a number of different regulatory pathways for ATMPs, depending on the product's characteristics and the target patient population. These pathways can be used to accelerate the development and approval of ATMPs, while still ensuring the safety and efficacy of these products. This abstract delves into the landscape of regulatory considerations surrounding ATMPs in the EU. It highlights the current Regulatory framework, approval pathways for marketing authorisation, European Medicines Agency (EMA) and its Committee for Advanced Therapies (CAT) evaluation process. The abstract navigates through the diverse regulatory pathways available for ATMPs, from clinical trials to market authorization. It underscores the synergy between innovation and patient welfare by exploring the priority medicines (PRIME) scheme introduced by the EMA. By examining the dynamic interplay between evolving scientific advancements and regulatory vigilance, this abstract

illuminates the strategic maneuvers and collaborative efforts driving the regulatory considerations shaping the future of ATMPs in the EU.

Keywords: Committee for Advanced Therapies, Certification, Evaluation, PRIME, Regulatory framework

INTRODUCTION:

These innovative treatments, which encompass gene therapies, cell therapies, and tissue-engineered products, hold the potential to revolutionize the way we address complex medical conditions. However, with great promise comes the responsibility to ensure patient safety, efficacy, and the maintenance of rigorous quality standards. In the European Union (EU), the regulatory landscape governing ATMPs has been carefully designed to address these challenges while fostering innovation. This essay delves into the intricate regulatory considerations that underpin the regulatory framework, classification, certification, evaluation, approval oversight of ATMPs in the EU. By exploring the multifaceted approaches taken by regulatory authorities, we gain insights into how these novel therapies are scrutinized and brought to patients in a manner that balances scientific progress with patient well-being **[1]**. The regulatory framework for medicinal products, instituted by the European Commission (EC), is executed through collaborative efforts between the European Medicines Agency (EMA) and the regulatory bodies within each EU member state. In recent times, a significant emphasis for the EMA, as well as regulatory bodies in the United States and Japan, has been to create and implement strategies aimed at accelerating the progress of clinical development **[2]**.

Advanced Therapy Medicinal Products (ATMP):

Advanced Therapy Medicinal Products (ATMPs) represent a category of innovative medical therapies that encompass gene therapies, cell therapies, and tissue-engineered products. These groundbreaking treatments hold tremendous potential for addressing various challenging and previously untreatable diseases and conditions **[3]**.

The Current Regulatory Framework of ATMP:

In 2009, the European Medicines Agency (EMA) established the Committee for Advanced Therapies (CAT) following the implementation of Regulation 1394/2007. CAT was created to address the innovative nature of Advanced Therapy Medicinal Products (ATMPs). To ensure a unified market access across Europe, the centralized procedure for marketing authorization applications (MAAs) became mandatory for

ATMPs, streamlining the evaluation process.

This Regulation establishes precise regulations governing the authorization, oversight, and pharmacovigilance of advanced therapy medicinal products. Furthermore, in conjunction with the definitions outlined in Article 1 of Directive 2001/83/EC and Article 3, points of Directive 2004/23/EC, the subsequent definitions shall be in effect for the intents and purposes of this Regulation.

(a) The term 'Advanced Therapy Medicinal Product' pertains to any of the subsequent medicinal products designed for human use:

- A gene therapy medicinal product, as described in Part IV of Annex I to Directive 2001/83/EC.
- A somatic cell therapy medicinal product, as outlined in Part IV of Annex I to Directive 2001/83/EC.

(b) 'Tissue engineered product' refers to a product that:

- Contains or comprises of manipulated cells or tissues. Is presented with attributes suitable for, or is employed in, or administered to humans with the purpose of regenerating, repairing, or substituting human tissue.

(c) Cells or tissues are categorized as 'engineered' if they satisfy at least one of these conditions:

- They have undergone substantial manipulation to achieve biological traits, physiological functions, or structural attributes relevant to the intended regeneration, repair, or replacement. Notably, manipulations listed in Annex I are not regarded as substantial manipulations.

(d) 'Combined Advanced Therapy Medicinal Product' signifies an advanced therapy medicinal product that fulfils the subsequent criteria:

- It integrates one or more medical devices, as an intrinsic component of the product, according to Article 1(2)(a) of Directive 93/42/EEC or one or more active implantable medical devices according to Article 1(2)(c) of Directive 90/385/EEC **[4]**.

In 2016, the EMA introduced the PRIority MEdicines (PRIME) scheme to expedite the development of medicines targeting unmet medical needs, facilitating faster patient access. The PRIME scheme provides active support for the efficient development of agents for such needs without requiring extensive datasets **[5]**. However, this accelerated pathway necessitates more stringent post-market safety and efficacy evaluations. While the CAT oversees ATMP regulation at the European level, the approval, evaluation, and monitoring of clinical trials fall under the responsibility of individual EU member states (MS) **[6]**.

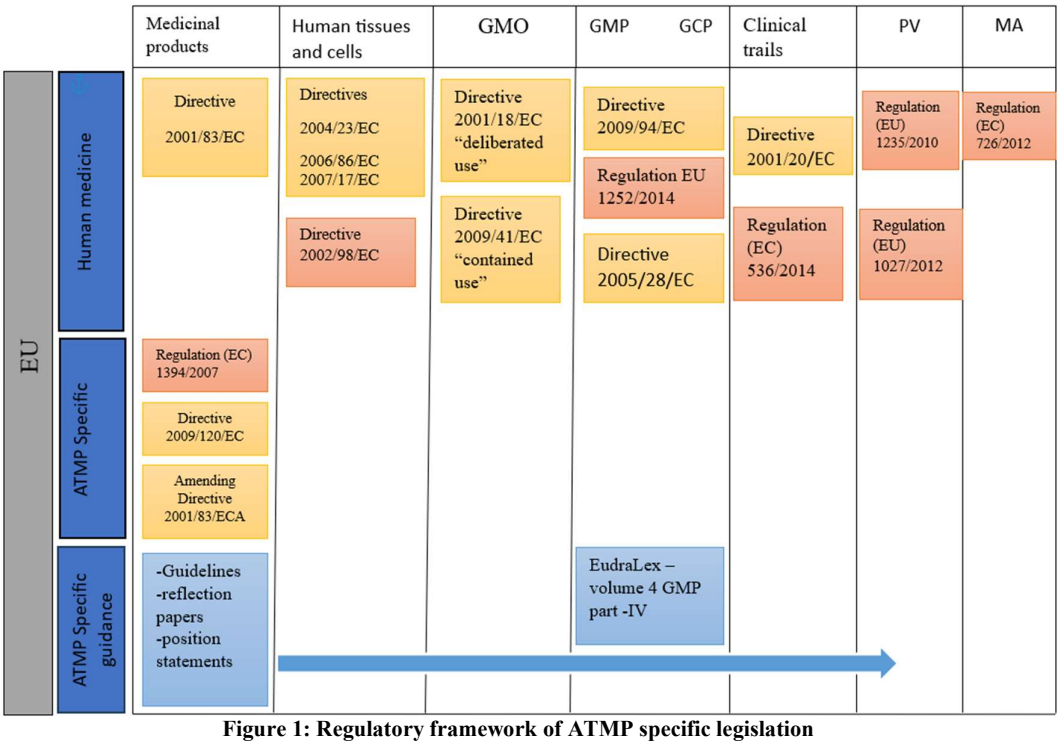

Figure 1: Regulatory framework of ATMP specific legislation

Regulatory approval pathways for ATMP:

Priority Medicines (PRIME) Designation: This program was developed in 2016 and was intended to enhance the support given for the development of medicines that target an unmet medical need. It uses processes that were already part of the regulatory framework such as accelerated assessment, conditional approval, and scientific advice. Medicines under this scheme are usually granted Accelerated Assessment. This assessment is a process that reduces the time required for an application to be reviewed (150 from the standard 210 days).

Conditional Marketing Authorisation (CMA):

This scheme was developed for medicinal products with promising, yet incomplete efficacy data are granted market authorisation on the condition that they are further evaluated while on the market. The CMA is only effective for one year. Upon review of information collected during the conditional approval period, these medicinal products may be withdrawn from the market, granted traditional standard approval or continue to be marketed conditionally, depending on the data collected during that period. The CMA scheme was launched in 2006, however it was later integrated within PRIME.

Authorisation Under Exceptional Circumstances (ECMA):

A marketing authorisation under exceptional circumstances is only applicable to therapies that cannot obtain a standard marketing authorisation as the required

safety and efficacy data cannot be provided due to the disease being so rare or because a clinical endpoint is challenging to measure due to ethical or scientific reasons. Since it is not possible for these therapies to obtain a standard MA, an ECMA is granted on the basis that the applicant agrees to continuously monitor product safety and reports any product incidents to the competent authorities. After an ECMA is granted, it is valid for five years with annual re-assessment procedures performed.**[7]**

Accelerated Assessment:

Accelerated assessment expedites the review period for marketing-authorization applications within the purview of the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP). Eligibility for accelerated assessment hinges on the CHMP's determination that the product holds substantial importance for public health and therapeutic advancement. The evaluation of marketing-authorization applications, as part of the centralized procedure, extends up to 210 days, excluding instances when applicants extend the timeline by providing supplementary data. Upon formal request and provision of substantial justification for acceleration, the CHMP can truncate this period to 150 days. Such acceleration requests should be submitted a minimum of two to three months before the actual application.**[8]**

ATMP Classification Procedure:

In the European Union, the scientific recommendation on classification of Advanced therapy medicinal products (ATMPs) is called ATMP classification. Where ATMP classification is an optional procedure for applicants, it involves committee of Advanced therapies (CAT).

The ATMP classification request is applicable solely to products that based on genes, cells, or tissues as their starting material, active substance, or finished product, including combinations with medical devices, bio-materials. This request is intended for cases where there are uncertainties about whether these products fall under the definition of an ATMP. If these products meet the criteria for ATMP, the Committee for Advanced Therapies (CAT), in its scientific recommendation, determines whether they qualify as gene therapy medicinal products, somatic cell therapy medicinal products, or tissue-engineered products. **[9]**

The applicant is required to submit two documents based on the templates provided on the ATMP classification EMA webpage:

- Administrative information
- Classification request form and briefing information, which should contain the following details:

1. Product information, including active substance, finished product,

mechanism of action, and proposed use.

2. Development information of the product, including manufacturing elements, quality aspects, and an outline of non-clinical and clinical development, all relevant to the ATMP classification.**[10]**

The purpose of this procedure is to enable applicants to clarify any uncertainties regarding, whether a product is based on genes, cells, or tissues aligns with the scientific criteria defining Advanced Therapy Medicinal Products (ATMPs). The purpose of this procedure is to enable applicants to clarify any uncertainties regarding, whether a product is based on genes, cells, or tissues aligns with the scientific criteria defining Advanced Therapy Medicinal Products (ATMPs). The aim is to address potential questions of borderline cases with other fields, such as cosmetics or medical devices, at an early stage, which may arise as scientific knowledge progresses.

It is highly advised that this clarification process takes place before submitting requests for scientific advice or protocol assistance, undergoing the Paediatric Investigation Plan (PIP) evaluation, seeking orphan drug designation, or applying for Marketing Authorisation Application (MAA) **[11].**

ATMP Certification:

The Committee for Advanced Therapies (CAT), a division of the European Medicines Agency (EMA), offers a certification process tailored for advanced therapy medicinal products (ATMPs) that are being developed by micro-, small-, and medium-sized enterprises (SMEs). This certification procedure presents SMEs with an opportunity to have their generated data assessed scientifically, ensuring their development is on a promising trajectory.**[12]**

Through this procedure, the CAT evaluates the quality data and, if available, non-clinical data produced by SMEs during any phase of their ATMP development. The primary goal is to proactively identify potential issues at an early stage, allowing SMEs to address these matters before submitting a marketing authorization application. Upon evaluation, the CAT might suggest granting a certification that confirms the alignment of the available data with the standards required for evaluating a marketing authorization application. Subsequent to the CAT's recommendation, the EMA issues the official certification.**[13]** The entire process of evaluation and certification is designed to be completed within a span of 90 days. This certification procedure is established by Article 18 of Regulation (EC) No 1394/2007, commonly known as the 'ATMP Regulation'.

The certification procedure focuses exclusively on the scientific evaluation of existing experimental data associated with the product. This provides companies with a snapshot of how their data align with the review standards of a Marketing Authorisation Application (MAA. The certification process does not aim to offer advice for further product development; such guidance should be sought through the scientific advice procedure.**[14]**

Evaluation Of Marketing Authorisation:

The European Medicines Agency (EMA) shoulders the responsibility of conducting scientific assessments for marketing authorization applications pertaining to advanced therapy medicinal. products (ATMPs) across the European Economic Area. Prior to formally submitting a marketing authorization application, companies have the option to secure confirmation from the EMA, affirming that their developmental medicine aligns with the scientific benchmarks that categorize it as an ATMP.

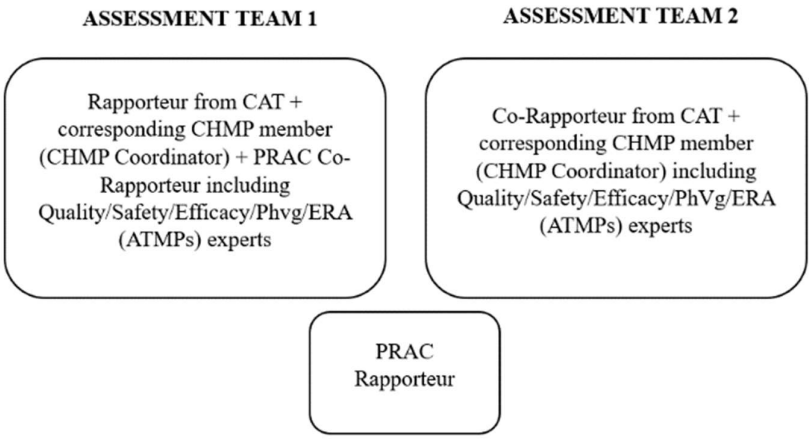

Figure 3: Assessment teams in ATMP evaluation

During the evaluation process of an initial marketing authorization application for an Advanced Therapy Medicinal Product (ATMP), two assessment teams are designated as follows:

- The initial assessment team comprises the CAT Rapporteur, the CHMP Coordinator, and a Co-Rapporteur from the Pharmacovigilance Risk Assessment Committee (PRAC).
- The second assessment team comprises the CAT Co-Rapporteur and the CHMP Coordinator **[15]**.

Additionally, a Rapporteur is selected from the members and substitutes of the PRAC to fulfil the role of overseeing pharmacovigilance aspects. The evaluation

of a Marketing Authorization (MA) application for Advanced Therapy Medicinal Products (ATMPs) in the European Union (EU) follows a comprehensive and rigorous process to ensure the safety, quality, and efficacy of these innovative therapies. The European Medicines Agency (EMA) is the central regulatory agency responsible for evaluating and granting MAs for ATMPs. Here is an overview of the evaluation process:**[16]**

Validation: Upon submission of the Marketing Authorization Application (MAA), the EMA conducts an initial review to ensure that the application is complete and includes all necessary data and documentation.

Scientific Evaluation: The Committee for Advanced Therapies (CAT), a specialized committee within the EMA, conducts a thorough scientific evaluation of the ATMP. The CAT assesses data from pre-clinical studies, clinical trials, manufacturing processes, and quality control to determine the overall benefit-risk profile of the product.

Assessment Report: The CAT prepares an assessment report that includes its evaluation of the ATMP's quality, safety, and efficacy. The report highlights any potential benefits and risks associated with the therapy.

Interaction with Applicant: The CAT may engage in interactions with the applicant during the evaluation process. This can include requesting additional information or clarifications to address any concerns or questions that arise from the assessment.

Scientific Advice: Developers can seek scientific advice from the EMA and the CAT at various stages of development. This advice helps ensure that the data collected aligns with regulatory expectations and requirements **[17]**.

Committee Feedback and Recommendations: The CAT provides its feedback and recommendations to the Committee for Medicinal Products for Human Use (CHMP), another key committee within the EMA. The CHMP is responsible for making the final decision on the marketing authorization **[18]**.

CHMP Evaluation: The CHMP reviews the CAT's assessment report and recommendations. It considers the scientific evidence, benefit-risk assessment, and the therapeutic need for the ATMP.

CHMP Opinion: Based on its evaluation, the CHMP provides an opinion on whether the ATMP should be granted marketing authorization. The opinion includes a recommendation for approval or refusal and may also include specific conditions for use, risk minimization measures, or requirements for additional post-authorization studies.

European Commission Decision: The European Commission, which is the executive body of the EU, makes the final

decision on whether to grant the Marketing Authorization based on the CHMP's opinion. The Commission takes into account the CHMP's recommendation, as well as any additional considerations related to public health and policy **[19]**.

Post-Authorization Monitoring: Once an ATMP receives marketing authorization, ongoing post-marketing surveillance and monitoring continue to ensure the product's safety and effectiveness in real-world settings. Regulatory agencies may take actions if new safety concerns emerge **[20]**.

CONCLUSION:

The regulatory considerations for Advanced Therapy Medicinal Products (ATMPs) within the European Union (EU) reflect a comprehensive and meticulous approach aimed at ensuring the safety, quality, and efficacy of these cutting-edge therapies. The regulatory framework, overseen by the European Medicines Agency (EMA), is specifically designed to accommodate the unique challenges posed by gene therapies, cell therapies, and tissue-engineered products. ATMPs undergo a stringent evaluation process that involves multiple specialized committees, including the Committee for Advanced Therapies (CAT) and the Committee for Medicinal Products for Human Use (CHMP). As the field of advanced therapies continues to progress, the EU's regulatory framework for ATMPs serves as a global benchmark, fostering innovation, promoting patient access to groundbreaking treatments, and exemplifying a harmonious balance between scientific progress and regulatory diligence.

ACKNOWLEDGMENT

All the authors are appreciated for their contribution and synthesis of the manuscript.

CONFLICT OF INTEREST

Authors declare no conflict of interest amongst themselves

REFERENCES

[1] Corbett MS, Webster A, Hawkins R, Woolacott N. Innovative regenerative medicines in the EU: a better future in evidence. BMC medicine. 2017 Dec; 15:1-8.

[2] Detela G, Lodge A. EU regulatory pathways for ATMPs: standard, accelerated and adaptive pathways to marketing authorisation. Molecular Therapy-Methods & Clinical Development. 2019 Jun 14; 13:205-32.

[3] Yu TT, Gupta P, Ronfard V, Vertès AA, Bayon Y. Recent progress in European advanced therapy medicinal products and beyond. Frontiers in bioengineering and biotechnology. 2018 Sep 21; 6:130.

[4] Ancans J. Cell therapy medicinal product regulatory framework in Europe and its application for MSC-

based therapy development. Frontiers in immunology. 2012 Aug 14; 3:253.

[5] Pizevska M, Kaeda J, Fritsche E, Elazaly H, Reinke P, Amini L. Advanced therapy medicinal products' translation in Europe: a developers' perspective. Frontiers in Medicine. 2022 Feb 3; 9:757647.

[6] Nagai S. Flexible and expedited regulatory review processes for innovative medicines and regenerative medical products in the US, the EU, and Japan. International journal of molecular sciences. 2019 Aug 3;20(15):3801.

[7] Warreth S, Harris E. The regulatory landscape for ATMPs in the EU and US: A comparison. Level 3. 2020;15(2):5.

[8] https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/accelerated-assessment (Accessed on 28-07-2023).

[9] Iglesias-López C, Agustí A, Obach M, Vallano A. Regulatory framework for advanced therapy medicinal products in Europe and United States. Frontiers in pharmacology. 2019 Aug 30; 10:921.

[10] https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/advanced-therapies/advanced-therapy-classification (Accessed on 31-07-2023)

[11] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/procedural-advice-provision-scientific-recommendation-classification-advanced-therapy-medicinal/2007_en.pdf (Accessed on 01-08-2023).

[12] Klug B, Celis P, Carr M, Reinhardt J. Regulatory structures for gene therapy medicinal products in the European Union. In Methods in Enzymology 2012 Jan 1 (Vol. 507, pp. 337-354). Academic Press.

[13] Flory E, Reinhardt J. European regulatory tools for advanced therapy medicinal products. Transfusion Medicine and Hemotherapy. 2013 Dec 1;40(6):409-12.

[14] Ham RM. Development, market authorization and market access of gene and cell-based therapies (Doctoral dissertation, Utrecht University).

[15] Chowdhury N. Regulation of nanomedicines in the EU: distilling lessons from the paediatric and the advanced therapy medicinal products approaches.

Nanomedicine. 2010 Jan;5(1):135-42.

[16] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/procedural-advice-evaluation-advanced-therapy-medicinal-product-accordance-article-8-regulation-ec/2007_en.pdf (Accessed on 02-08-2023).

[17] de Wilde S, Coppens DG, Hoekman J, de Bruin ML, Leufkens HG, Guchelaar HJ, Meij P. EU decision-making for marketing authorization of advanced therapy medicinal products: a case study. Drug discovery today. 2018 Jul 1;23(7):1328-33.

[18] Rousseau CF, Mačiulaitis R, Śladowski D, Narayanan G. Cell and gene therapies: European view on challenges in translation and how to address them. Frontiers in Medicine. 2018 May 28;5:158.

[19] Fürst-Ladani S, Bührer A, Fürst W, Schober-Ladani N. Regulatory Aspects for Approval of Advanced Therapy Medicinal Products in the EU.

[20] Gomes KL, da Silva RE, da Silva Junior JB, Bosio CG, Novaes MR. Post-marketing authorisation safety and efficacy surveillance of advanced therapy medicinal products in Brazil, the European Union, the United States and Japan. Cytotherapy. 2023 Jul 12.