Regulatory considerations for cellular and gene therapy products in EU and US: A comparative analysis

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Advanced therapy medicinal products (ATMPs)/Cellular and gene therapy (CGT) products

These are innovative and complex biological products, which in most cases require extensive and complex clinical and preclinical developments. Regulatory authorities are actively trying to ensure a good regulatory environment for these products as they are resulting in potential therapies that may help treat many unmet medical diseases and conditions. Therefore, sponsors (industry, academia, government agencies, and other groups) are seeking to understand how to develop a product from the discovery stage to clinical research, and hopefully, to licensure. As regulatory agencies are involved in the oversight of these promising products, we recognized the importance of sharing the details of regulatory aspects of the two biggest regions working on these products, that is, the European Union and the United States.

Table 1. Regulations and legislations for ATMPs/CGTs

<table>
<thead>
<tr>
<th>European Union</th>
<th>United States</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATMP is a common term in regulatory documents and legislation.</td>
<td>On the contrary, such products are categorized and collectively referred to as CGT products</td>
</tr>
<tr>
<td>Directive 2001/83/EC (relating to medicinal products for human use)</td>
<td>FDCA and the Public Health Services Act Section 351 of PHS (Biologics)²</td>
</tr>
<tr>
<td>ATMPs are licensed under article 8.3 of this section¹</td>
<td>21 Code of Federal Regulations Title 21 CFR Parts 600 - 680 (Requirements for biological products) and Title 21 CFR 1271 (Biologicals and medical devices)⁴</td>
</tr>
</tbody>
</table>

ATMP: Advanced therapy medicinal product; CGT: Cellular and gene therapy; EC: European Commission; FDCA: Federal Food, Drug, and Cosmetic Act

Overview

Considering the unconventional nature of these therapies and their approval pathways, it is advisable for sponsors to seek opinions of regulatory bodies as early as possible. To facilitate this, the regulatory bodies of Europe and United States have developed special programs for the benefit of sponsors and patients. This article focuses on the comparison of regulatory framework covering a glimpse of regulations, approval pathways, and various incentives related to ATMPs/CGTs in the European Union and the United States.

Table 1 refers to the regulations and legislations applicable for these products in these regions.

In January 2020, the Food and Drug Administration (FDA) released six final guidance documents on gene therapy manufacturing and clinical development, including one draft guidance, “Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations,” and two more guidelines on CGT products in 2021⁵. The European Medicines Agency (EMA) has also published various guidelines specific to ATMPs such as questions and answers on comparability considerations for ATMPs (EMA/CAT/499821/2019) and a draft guideline on the safety and efficacy follow-up – risk management of ATMPs and so on⁶.
While these lists are not exhaustive, the regulators are also supporting accelerated development of these products by their active participation and interaction with sponsors, provision of scientific advice, fast track approval, and various drug designation schemes as the products go through each milestone during the life cycle. Further, the EMA addresses the unique needs of micro-, small-, and medium-sized enterprises (SMEs) through the SME office. A user guide is available on the administrative and procedural aspects of the provisions laid down in Regulation (EC) No 726/2004 that are relevant to SMEs. Fig. 1 illustrates the key regulatory milestones for the ATMPs/CGTs during the life cycle.

ATMP: Advanced therapy medicinal product; CMA: Conditional Marketing Authorisation; EMA: European Medicines Agency; FDA: Food and Drug Administration; ITF: Innovation Task Force; MAA: Marketing authorization application; PIP: Pediatric Investigation Plan; PRIME: PRiority Medicines; PSP: Pediatric Study Plan; RMAT: Regenerative Medicine Advanced Therapy; INTERACT: INitial Targeted Engagement for Regulatory Advice on CBER products; IND: Investigational New Drug; BLA: Biologics License Application
Pre-classification application

To ensure a correct classification of ATMP/CGT, the regulatory bodies of Europe and United States have created a provision of giving scientific advice to the applicants. There is a requirement of submitting some minimum information and data to obtain a proper classification. Such classification procedures help in addressing specific issues related to ATMP/CGT development, especially related to combined ATMPs/CGTs or combination products. It is advisable to obtain correct classification during early development stage, followed by the development of the product per established guidelines. A comparison of such means of requesting a classification in both the geographies is provided in Table 2.

Table 2. Requesting a classification to regulatory authorities

<table>
<thead>
<tr>
<th>European Union</th>
<th>United States</th>
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<tbody>
<tr>
<td><strong>Advanced therapy classification</strong></td>
<td><strong>Request for designation</strong>[^2]</td>
</tr>
<tr>
<td>• The EMA establishes the procedure to address questions on borderline classification[^1]</td>
<td>• Determination of the regulatory identity of a product as a drug, device, or biologic or combination product.</td>
</tr>
<tr>
<td>• The CAT of the EMA delivers scientific recommendations on the ATMP classification[^1,^2]</td>
<td>• The OCP assigns review responsibility for combination products to a lead center.</td>
</tr>
<tr>
<td>The CAT establishes guideline on ATMP data certification for SMEs only[^10]</td>
<td></td>
</tr>
<tr>
<td>• It provides scientific certainty to sponsor (whether the development is on track for obtaining MA).</td>
<td></td>
</tr>
<tr>
<td>• It requires early quality/development data and early nonclinical data.</td>
<td></td>
</tr>
<tr>
<td>• 90 days procedure</td>
<td></td>
</tr>
<tr>
<td><strong>For cATMPs:</strong> Medical device is evaluated by notified bodies in the European Union as part of CE certification[^11]</td>
<td></td>
</tr>
</tbody>
</table>

[^1]: European Medicines Agency (EMA)
[^2]: Office of Combination Products (OCP)
[^10]: Small and medium enterprises

ATMP: Advanced therapy medicinal product; cATMPs: Combined advanced therapy medicinal product; CAT: Committee of Advanced Therapies; CE: Conformité Européenne; EMA: European Medicines Agency; MA: Marketing authorization; OCP: Office of Combination Products; SMEs: Small and medium enterprises
Regulatory organizations for advanced therapy medicinal products/cellular and gene therapies

Different committees/centers are responsible for classifying, reviewing, and approving the ATMPs/CGTs in both the geographies. Table 3 summarizes the glimpse of the official bodies involved in the ATMP/CGT regulatory processes.

Table 3. Official bodies involved in regulatory processes

<table>
<thead>
<tr>
<th>European Union</th>
<th>United States</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CAT</strong>&lt;sup&gt;13&lt;/sup&gt;: Responsible for • reviewing applications for MA • classification of ATMP • certification and scientific advice on ATMP</td>
<td><strong>CBER</strong>&lt;sup&gt;13&lt;/sup&gt;: Responsible for • ensuring the safety, purity, potency, and effectiveness of many biologically derived products, including advanced therapy</td>
</tr>
<tr>
<td><strong>CHMP</strong>&lt;sup&gt;15&lt;/sup&gt;: Responsible for elaborating the opinions of the agency on all issues regarding medicinal products for human use</td>
<td><strong>OTAT (within CBER)</strong>&lt;sup&gt;13,16&lt;/sup&gt;: OTAT comprises of five divisions. The Division of Cellular and Gene Therapies is responsible for • discussion of each regulated product type, outreach, sponsor interaction, and research</td>
</tr>
<tr>
<td><strong>EC</strong>&lt;sup&gt;14&lt;/sup&gt;: Responsible for • authorizing body for all centrally authorized products • taking a legally binding decision based on the recommendation of the EMA</td>
<td><strong>FDA</strong>&lt;sup&gt;17&lt;/sup&gt;: • Legal authority to authorize human medicinal products</td>
</tr>
</tbody>
</table>

ATMP: Advanced therapy medicinal product; CAT: Committee of Advanced Therapies; CBER: Centre for Biologics Evaluation and Research; CHMP: Committee of Medicinal Products for Human Use; EC: European Commission; EMA: European Medicines Agency; FDA: Food and Drug Administration; MA: Marketing authorization; OCP: Office of Combination Products; OTAT: Office of Tissues and Advanced Therapies; RFD: Request for designation
Consultation meetings, parallel scientific advice, and cluster activities

The sponsors can also request informal consultation meetings, such as INitial Targeted Engagement for Regulatory Advice on CBER producTs (INTERACT) meeting and Innovation Task Force (ITF) briefing meetings with the FDA and the EMA. In the United States, the sponsors of the biological products regulated by the Centre for Biologics Evaluation and Research (CBER) can get a preliminary informal consultation for innovative investigational products with unique challenges through the INTERACT meeting program. In the European Union, ITF is a multidisciplinary group that includes scientific, regulatory, and legal competences. ITF briefing meetings facilitate informal exchange of information and guidance in the development process, complementing and reinforcing existing formal procedures such as ATMP classification and certification, designation of orphan medicinal products, and scientific advice. A parallel scientific advice can also be requested from the EMA and the FDA explicitly for advanced therapy products of special interest by their sponsors.\(^{18,19}\)

Advanced therapy medicinal products/cellular and gene therapies being complex products, meeting with the regulatory authorities can help sponsors to obtain legal and scientific feedback on the classification of the product, exchange of information, and recommendations on development, and thus, help accelerate the development process. Table 3 refers to these meetings in both regions.

Table 3. Various types of meetings between biopharmaceutical companies and regulators

<table>
<thead>
<tr>
<th>European Union</th>
<th>United States</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informal meetings between innovators and regulators</td>
<td>Informal meetings between innovators and regulators(^{19})</td>
</tr>
<tr>
<td>• ITF meetings with the EMA(^{20})</td>
<td>• INTERACT meetings with the FDA</td>
</tr>
<tr>
<td>• Informal meetings with NCA</td>
<td></td>
</tr>
<tr>
<td>Scientific advice or protocol assistance</td>
<td>preIND meetings with the FDA(^{21})</td>
</tr>
<tr>
<td>• With the EMA/NCA</td>
<td>• At any stage of development</td>
</tr>
<tr>
<td>• At any stage of the development a medicine</td>
<td>• Several types of meetings depending upon the scope and development phase (Type-A, Type-B [End of phase-1/2, SPA, pre-phase 3, pre-BLA meetings], or Type-C meetings)</td>
</tr>
<tr>
<td>• Applicable fee</td>
<td>• The FDA offers standalone CMC meetings for biologics</td>
</tr>
</tbody>
</table>

Clusters:

The clusters are areas of cooperation focusing on special topics and therapeutic areas identified as requiring an intensified exchange of information and collaboration. The EMA holds regular meetings with the non-EU regulatory authorities. The EMA, FDA, and Health Canada participate in cluster activities for ATMPs, and their meetings also coincide with the Committee of Advanced Therapies (CAT) meetings. The key objective is to harmonize the regulatory approach of these products. The information exchanged includes marketing authorization applications (MAAs), extension of indications, risk-management plans, and safety signals. The documents such as scientific advice; ATMP classification reports; assessment reports of marketing-authorization applications from the EMA and Investigational New Drug (IND), pre-IND, and pre-biologics-license-application; and minutes of meeting from the FDA are also exchanged. Both agencies also share their draft guidelines.

Incentives for development of therapeutics intended to treat rare diseases:

To encourage the research interest of the industry in such developments, regulatory agencies generally provide incentives. Such incentives from European and US regulatory authorities are discussed and compared in Table 4.

Table 4. Incentive schemes for treatment of rare diseases

<table>
<thead>
<tr>
<th>European Union</th>
<th>United States</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ODD</strong>23–26: Orphan drugs are developed to treat rare medical conditions, and they cater to very less population. Hence, due to less profit, European and US regulatory agencies provide several advantages as discussed below:</td>
<td></td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td><strong>Advantages</strong></td>
</tr>
<tr>
<td>• Applicable to medicinal products only</td>
<td>• Applicable to drugs, medical devices, special foods</td>
</tr>
<tr>
<td>• Significant benefit to be demonstrated in the application</td>
<td>• Significant benefit not necessarily be demonstrated at the time of application</td>
</tr>
<tr>
<td>• Applicable for life-threatening or chronically debilitating condition</td>
<td>• Not necessary for life-threatening or chronically debilitating condition</td>
</tr>
<tr>
<td>• Provides market exclusivity of 10 years</td>
<td>• Provides market exclusivity of 7 years</td>
</tr>
<tr>
<td>• No fees for scientific advice</td>
<td>• Annual grant funding for CTs</td>
</tr>
<tr>
<td></td>
<td>• Tax credits for clinical research costs</td>
</tr>
<tr>
<td></td>
<td>• Assistance in designing clinical studies</td>
</tr>
<tr>
<td></td>
<td>• Waiver of the PDUFA fees</td>
</tr>
<tr>
<td><strong>Rare pediatric disease priority review vouchers</strong>27</td>
<td>The FDASIA section 529</td>
</tr>
<tr>
<td>• The FDA will award priority review voucher to sponsors of rare pediatric disease if the product meets certain criteria.</td>
<td>• Sponsor that can receive approval under these criteria will qualify for the voucher, which can be redeemed to receive priority review of a subsequent MA application.</td>
</tr>
</tbody>
</table>

CT: Clinical trial; FDA: Food and Drug Administration; FDASIA: Food and Drug Administration Safety and Innovation Act; MA: Marketing authorization; ODD: Orphan Drug Designations; PDUFA: Prescription Drug User Fee Act
Pediatric plans – conducting, deferring, or waiving pediatric studies

Some rare disease conditions affect pediatric population, and thus, it is important to understand pediatric clinical study plan. It comes into picture when an applicant has significant clinical data in adult population. Table 5 describes the regulations and details regarding pediatric studies in both the regions.

Table 5. Pediatric studies in the European Union and the United States

<table>
<thead>
<tr>
<th>European Union</th>
<th>United States</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Termed as PIP\textsuperscript{28}</td>
<td>• Termed as PSP\textsuperscript{29}</td>
</tr>
<tr>
<td>• Can be initiated at the end of Phase I CT</td>
<td>• Can be initiated at the end of Phase II CT</td>
</tr>
<tr>
<td>• No waiver or exemption for ODD</td>
<td>• Exempted for ODD, except for cancer indication</td>
</tr>
<tr>
<td>• PDCO: Committee is responsible to assess PIPs and provides opinion on the quality, safety, or efficacy of a medicine for use in pediatric populations, at the request of CHMP.</td>
<td>• PeRC\textsuperscript{30}: Provides consultation and general review of pediatric information submitted to the agency.</td>
</tr>
</tbody>
</table>

CT: Clinical trial; CHMP: Committee of Medicinal Products for Human Use; EC: European Commission; ODD: Orphan Drug Designations; PDCO: Paediatric Committee; PeRC: Pediatric Review Committee; PIP: Paediatric Investigation Plan; PREA: Pediatric Research Equity Act; PSP: Pediatric Study Plan

Marketing authorization approval pathways:

Like all other medicinal products, MA approval pathways for ATMPs/CGTs are also available. These are dependent on product type and targeted population. The regulatory pathways for ATMPs/CGTs are important to understand since they are mostly developed for orphan diseases, to treat highly unmet medical needs, and to avail early access to treat patients suffering from life-threatening diseases. To address these requirements, regulatory agencies provide expedited pathways and some attractive advantages to the sponsor. Such pathways for both EU and US regions are discussed in Table 6.

Table 6. Marketing authorization (MA) approval pathways

<table>
<thead>
<tr>
<th>European Union\textsuperscript{31,32}</th>
<th>United States\textsuperscript{33-35}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Termed as “Marketing Authorisation Application (MAA)”</td>
<td>Termed as “Biologics License Application (BLA)”</td>
</tr>
<tr>
<td>ATMPs are evaluated via CP, single MA valid in the European Union.</td>
<td>All medicines are evaluated at a centralized level.</td>
</tr>
<tr>
<td>The centralized MA is recommended by the EMA and granted by the EC.</td>
<td>BLA is granted by the FDA.</td>
</tr>
<tr>
<td>MA types can be</td>
<td></td>
</tr>
<tr>
<td>1. standard MA</td>
<td></td>
</tr>
<tr>
<td>2. conditional MA</td>
<td></td>
</tr>
<tr>
<td>3. MA under exceptional circumstances</td>
<td>Types:</td>
</tr>
<tr>
<td>1. standard BLA</td>
<td></td>
</tr>
<tr>
<td>2. accelerated approval</td>
<td></td>
</tr>
</tbody>
</table>

ATMP: Advanced therapy medicinal product; BLA: Biologics License Application; CP: Centralized procedure; EC: European Commission; EMA: European Medicines Agency; FDA: Food and Drug Administration; MA: Marketing authorization
PRIME Designation\textsuperscript{36,37}  
Development of medicines that target unmet medical need and can be applied during early development.  
Advantages  
• Provides accelerated assessment: Standard timeline is 210 days, whereas accelerated assessment timeline has been shortened to 150 days  
• A rapporteur from CHMP/CAT is appointed, which will provide continuous development during development/MAA  
• Kick-off meeting that helps in overall development and regulatory strategy  
• Dedicated contact point  
• Scientific advice at key development milestone  
• Reduction of fees upon request

Breakthrough Therapy\textsuperscript{24}  
Development of drugs with potential to address an unmet medical need applied during early development  
Expedites development and review process  
Advantages  
• Intensive guidance designing efficient development  
• A senior FDA staff will be involved

Conditional MA (early access – impact in the development time in MA)\textsuperscript{37}  
• Applicable for seriously debilitating/life-threatening disease and ODD  
• To be used in emergency health situation/public health threats  
• MA granted before comprehensive clinical data are available  
• Need to fulfill obligations (viz. ongoing or new studies or collecting additional data to confirm the benefit–risk balance of the medicine remains positive)  
• CMA valid for 1 year (annual renewals should be done)  
• Switch to MA when comprehensive data are submitted (can be done during renewal or new procedure)  
• Based on CHMP opinion, EC issues decision on “full” MA with standard 5-year validity

Fast Track Designation\textsuperscript{35}, Applicable to the products that  
• treat serious condition,  
• show improved/superior effectiveness, or  
• address an unmet medical need

AP\textsuperscript{38}: Can be considered due to following  
• Approval in well-defined patient subgroup with a high medical need and then widening of indication to larger population  
• Early regulatory approval (i.e., conditional approval)

Eligibility criteria  
• Iterative development plan (expansion target vs. reduction on uncertainty)  
• Monitoring, collection, and use of post-approval real world clinical data  
• High unmet medical need

<table>
<thead>
<tr>
<th>Table 6. Drug designations and expedited development schemes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>European Union\textsuperscript{31,32}</strong></td>
</tr>
<tr>
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<td>• Scientific advice at key development milestone</td>
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</tr>
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Eligibility criteria  
• Iterative development plan (expansion target vs. reduction on uncertainty)  
• Monitoring, collection, and use of post-approval real world clinical data  
• High unmet medical need

**Brexit changes**

In Northern Ireland, these products will continue to be regulated in accordance with the Centrally Authorised Procedure of the EMA and will be regulated nationally in Great Britain by the Medicines and Healthcare products Regulatory Agency (MHRA) in accordance with the previous principles. Definitions will remain unchanged, and classification will be followed according to the current EU guidance Reflection paper on classification of advanced therapy medicinal products (EMA/CAT/600280/2010 rev.1). Sponsors can fill the ATMP advice form and seek further guidance from the MHRA if they are uncertain about the classification of their products.43

**Discussion**

With the introduction of new technologies and scientific advancements, these products are being developed at a very fast pace but at increasing complexity with every new development, and thus, changing regulations as the regulators evolve in their understanding. The EMA and FDA are actively involved in multiple initiatives and are encouraging the development of these products. The regulators actively participate with industry in addressing key challenges during the product review (administration of the products), that is, the need for precision therapy programs such as appropriate training of the healthcare staff for patient care and whether these products will achieve the desired benefits ensuring safety and efficacy on a long-term basis. Scientific advice is provided by the EMA on quality and nonclinical and clinical development to generate robust evidence for regulatory submissions.44 The regulators also provide scientific advice and protocol assistance for the developers of designated orphan medicines to discuss compliance criteria such as demonstration of significant benefit. Therefore, early interaction with the regulators is crucial while developing promising treatments targeting rare diseases, though the innovators will also have to continuously align to dynamic regulatory requirements across the product life cycle.

APCER’s regulatory team supports in finalizing the appropriate strategies in various regulatory meetings and in getting the appropriate designations to gain early as well as easy access to the market.
**Glossary**

**For the EU market**

**Gene therapy products**: These contain genes that lead to a therapeutic, prophylactic, or diagnostic effect. They work by inserting “recombinant” genes into the body, usually to treat a variety of diseases, including genetic disorders, cancer, or long-term diseases. A recombinant gene is a stretch of deoxyribonucleic acid (DNA) that is created in the laboratory, bringing together DNA from different sources.

**Somatic-cell therapy medicinal products (SCTMPs)**: These contain cells or tissues that have been manipulated to change their biological characteristics or cells or tissues not intended to be used for the same essential functions in the body. They can be used to cure, diagnose, or prevent diseases.

**Tissue-engineered medicinal products (TEP)**: These contain cells or tissues that have been modified so they can be used to repair, regenerate, or replace human tissue.

**cATMPs**: In addition, some ATMPs may contain one or more medical devices as an integral part of the medicine, which are referred to as cATMPs. An example of this is cells embedded in a biodegradable matrix or scaffold.

**Substantial manipulation**: The cells or tissue(s) have been manipulated resulting in a change of their biological characteristics, physiological functions, or structural properties relevant for the intended therapeutic application.

**Homologous use**: Cells or tissues (whether substantially manipulated or not) are used to maintain the original function(s) in the same anatomical or histological environment.

**Different essential function or non-homologous use**: The cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor.

**For the US market**

**Human Gene Therapy Products**: All products that mediate their effects by transcription or translation of transferred genetic material or by specifically altering host (human) genetic sequences. Human gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use.

**Somatic cell therapy/cellular products**: Somatic cell therapy is defined as any autologous, allogeneic, or xenogeneic cells that have been propagated, expanded, selected, pharmacologically treated, or otherwise altered in biological characteristics ex vivo to be administered to humans and applicable to the prevention, treatment, cure, diagnosis, or mitigation of disease or injuries.

**Combination products**: A combination product is a product composed of any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device, and a biological product.

**“More than minimal manipulation”**: Structural tissues may contain both extracellular matrix and cellular components, and any alteration of these components that relates to the utility for reconstruction, repair, or replacement of the structural tissue generally would be considered more than minimal manipulation.

**Homologous use**: Homologous use means the repair, reconstruction, replacement, or supplementation of a recipient’s cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor, including when such cells or tissues are for autologous use.
References


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