Cell-Based Therapies in the EU: Post-Marketing Requirements, Market Landscape, and Challenges

Laura Beth Kupsch and Suman Jangid, University of Southern California, Los Angeles, CA, United States

Abbreviations

ATMPs Advanced Therapy Medicinal Products
CBMPs Cell-Based Medicinal Therapies
CAT Committee for Advanced Therapies
EMA European Medicines Agency
GTMPs Gene Therapy Medicinal Products
MAH Marketing Authorization Holder
NCA National Competent Authority
RMP Risk Management Plan
TEPs Tissue Engineered Products

Introduction

Few approved cell-based therapies have been available to patients, but the potential promise of these therapies has made them an attractive opportunity in healthcare. Cell-based therapies are regulated as "Advanced Therapy Medicinal Products (ATMPs)" in Europe. Regulatory authorities recognize the potential capability of cell-based therapies to address diseases with little or no current treatment. However they must balance the important goal of assuring access to these products with the appropriate oversight to assure that the available products are safe and effective. Because these products are nontraditional. While supporting the development of patient access to ATMPs, EMA has been carefully reviewing the risks/benefit profile of these products once they are available for treatment and implementing requirements for oversight.

Scope

This chapter will provide a comprehensive assessment of the EU laws, rules and guidelines to be followed for the post-marketing stage of ATMPs. These activities include specific aspects of post-approval activities including pharmacovigilance, risk management planning, and safety and efficacy follow-up of patients treated with such products. This chapter also provides an overview of products submitted for marketing authorization and subsequent outcomes. Not covered by this chapter are the development of ATMPs and the specific rules regarding: non-viable cells and cellular fragments; products containing genetically modified cells and tissues used for gene therapy specifically; combined ATMPs of gene therapies; xenogeneic cell-based therapies; or minimally manipulated cells for homologous use, that is, transfusions and transplants.

Post-Authorization Requirements

Due to their complex nature, ATMPs need additional safeguards and standards. Thus, ATMPs approved for marketing by the EMA typically will be subject to ongoing review and monitoring. As described in the EMA "Guideline on Safety and Efficacy Follow-up—Risk Management of Advanced Therapy Medicinal Products" (Regulation (EC) No. 1394/2007), Marketing Authorization Holders of ATMPs must have in place stringent pharmacovigilance and risk-management systems, as well as efficacy follow-up for patients receiving the approved medicinal product (Fig. 1). EMA recognizes that a comprehensive and fluid review of the product in the marketplace will help to inform the use and evaluation of ATMPs, and that additional guidelines and regulations may be required as regulatory reviews provide regulators with more experience. The EMA has encouraged interactive discussion with Marketing Authorization Holders (MAH) to ensure diligent review and oversight of an ATMP well beyond the timeframe of market approval.

The EMA has also created a guideline specifically to follow patients who have been treated with a GTMP (Guideline on Follow-Up of Patients Administered with Gene Therapy Medicinal Products, EMEA/CHMP/GTWP/60436/200). Further, Directive 2004/23/EC describes the expectations regarding the chain of custody for human tissues and cells, including standards necessary to maintain safety and quality. Both documents recognize the importance of extended oversight of patients and the need for specific requirements to describe how to link patients back to the manufacturing process for the ATMP over an extended period.

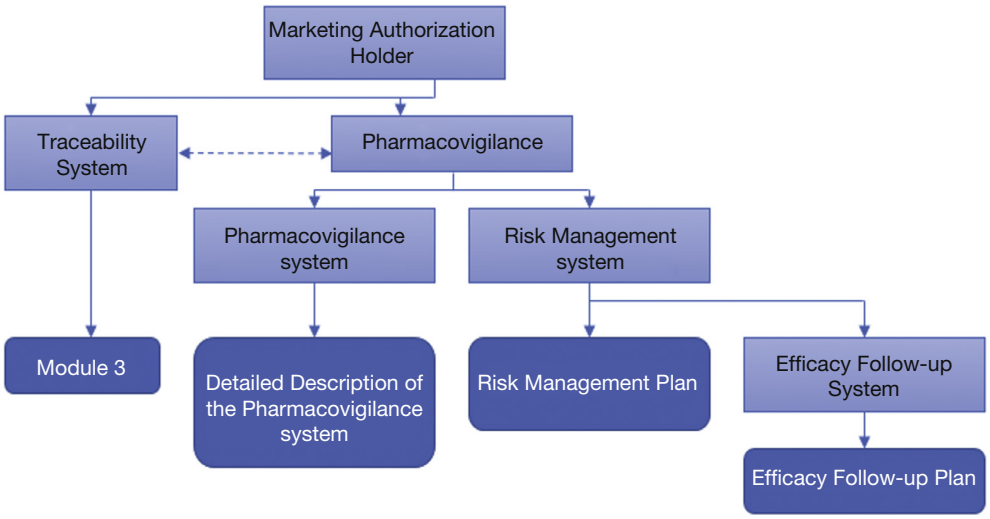

Fig. 1 Post-authorization surveillance of ATMPs. Reproduced from http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500006326.pdf.

It is not unusual for the Market Authorization Holders to be assigned significant post-marketing study commitments at the time when EMA approves a submission. They are expected to comply with all post-marketing requirements and to ensure that the data in the original dossier is updated so it remains current and relevant. The collected information is also used to update the risk/benefit profile, which will become important when planning additional studies or making changes to the manufacturing process, for example. Most of the approaches that will be used post-market are the same in principle as those in other regions of the world, but the rules and guidances may differ in specific respects. Three types of activities are of particular concern for ATMPs in the post-market period: post-market studies of safety and efficacy, risk management planning and execution and post-authorization vigilance.

Post-Authorization Studies: Considerations and Additional Requirements

Post marketing studies share the same challenges in Europe as in other regions, such as the US. EMA updated the "Guideline on safety and efficacy follow-up and risk management of Advanced Therapy Medicinal Products" in January 2018. The revised guideline is in draft stages and is expected to be finalized after end of a public consultation period estimated at the time of writing to be April 30, 2018. This recent revision to the guideline provides enhanced direction on how to design post-authorization safety and efficacy studies. Some assessments of product safety and efficacy may also be carried out as defined in the approved labeling and Summary of Product Characteristics (SmPC). For these post market assessments, standard of care practices should be used whenever possible to ease the burden on patients, care givers, and healthcare providers. Consideration must also be given to any ATMPs that require additional data from, for example, any living donors, tissue or cell procurement operations, or close contacts or offspring of the patient. The need to acquire data from individuals other than the recipient is considered during the marketing authorization process and is part of the traceability system to ensure that the long-term treatment profile of the ATMP is well-defined. Marketing Authorization Holders are expected to have plans for managing communication between all parties to assure appropriate data and information exchange.

The follow-up period for each patient will vary based on the characteristics of the ATMP but all Marketing Authorization Holders and healthcare providers are typically required to maintain clinical and traceability data for a minimum of 30 years post expiration of the product. Additional follow-ups and monitoring can be burdensome for patients, care-givers and involved medical staff. Therefore, the EMA has indicated that the specific follow-up period is to be determined from the known data and the anticipated duration of long-term side effects.

EU-Risk Management Plan

A central tenet for clinical use of ATMPs is the need to manage risk formally using a Risk Management Plan (RMP). Part of this plan should address the traceability of the medicinal product from the point at which a patient enters a clinical trial and for years after he or she receives the product as described above. The collected information will allow the risk assessments to be modified and the risk/benefit profile to be updated. This risk management plan will apply even when products are no longer pursued as commercially viable entities. Because the development and commercialization of ATMPs is a risky business proposition, not all developers can survive as a business entity after market approval. Notably, the EMA assumes responsibility for the risk management/traceability program for Marketing Application Holders that are no longer in business.

A robust RMP is created to provide additional information about the safety and efficacy of an ATMP. Data from the follow-up of patients in all clinical trials, observational studies and consumer use must be considered in the risk management system. The Follow-Up Guideline identified above describes the follow-up system as "any systematic collection and collation of data that is designed in a way that enables learning about safety and/or efficacy of an ATMP." The EMA has designated a specific module of the Risk Management Plan for ATMPs (Module SVII), which recognizes that "newly identified safety concerns" should be comprehensively reviewed and carefully identified, whether actual or potential. These include risks listed in the product labeling, as well as risks to the patient (or donor) that may typically occur and have an impact on quality of life or could become more serious. Risks to be listed are not limited to treatment-related risks, but may also include those related to immunosuppression, immunogenicity, infection, procedural interventions, medicinal product storage and handling, environmental implications, and rescue procedures. The RMP should summarize the risks known to occur with the ATMP and define risk mitigation opportunities and activities. The primary outcome of a risk management exercise is the control of risks, so the RMP should detail the methods that the Marketing Authorization Holder will pursue to control known risks and minimize these and other potential risks going forward. The Guideline on Safety and Efficacy Follow-up details possible systems that can be used, including specialized training and accreditation for health care providers, control of distribution of the ATMP only to appropriately accredited persons and harmonized communication to patients to help educate them about their treatment, including its risk. The Guideline also describes financial and regulatory penalties that a Marketing Authorization Holder may face if it fails to adhere to the agreed RMP.

Educational tools that provide information on adverse reactions and continuing care should be created to assist the patient in communicating appropriate information to caregivers and family. Marketing Authorization Holders are encouraged to work with healthcare providers to determine methods that decrease errors at the treatment level. Implementing control measures cannot guarantee that no problems will occur; therefore, a system to measure the effectiveness of the Risk Minimization Plan is needed. Metrics are captured for the risk interventions that are taken to determine if each method or system is effective, and where gaps in the system need to be handled.

Post-Authorization Surveillance

Post-authorization requirements such as safety reporting documentation (expedited safety reports and Periodic Safety Update Reports) and RMP updates help to ensure that safety is continuously reviewed, reported, and analyzed. The EMA utilizes the EudraVigilance Website as a method for Marketing Authorization Holders to share safety events with other stakeholders, including patients, healthcare providers, and other regulatory bodies. The website provides a systematic way to disclose safety data, and a standardized system for others to access data and evaluate it for safety signals or potential concerns. EMA has a system for post-marketing review of pharmacovigilance activities and conducts the appropriate inspections to determine if Marketing Authorization Holders are complying with directives, guidelines, and post-marketing obligations.

Patients with personalized ATMP treatments are particularly vulnerable to loss of personal information, considering that ATMP treatment is individualized and traceability systems can potentially suffer from privacy breaches. Recognizing this vulnerability, EMA permits the processing of personal health-related information when the patient or legal guardian has given proper consent, or when the data is necessary for health care reasons. The data in question must be appropriate for the intended purpose and cannot be used for other inappropriate reasons.

Labeling

Labeling is a key component to assure a secure supply chain and to identify safety-related issues. Proper control of the identification of medicinal products, tissues, and cells is imperative to know what each patient is being given. The labeling of the ATMP should reflect the Summary of Product Characteristics (SmPC) that was submitted and approved as part of the initial marketing authorization application and any subsequent approved amendments. According to the EMA, "the SmPC is the basis of information for healthcare professionals on how to use the medicinal product safely and effectively."

Summary of Product Characteristics (SmPC)

All documents pertaining to the use, development, safety, and precautions are derived from the approved SmPC. The SmPC and related documents, such as the label and package leaflet, are published once a marketing application is approved and made available for public review on the EMA website. As the key document from which others originate, the SmPC should be written in a way that is comprehensive, concise, and without ambiguity. It should be structured to reflect the use in the primary population for which the ATMP is intended, followed by specific information for additional populations (as applicable), and should not refer to other medicinal products. The SmPC should be version-controlled. It should include the following:

- Name and composition of the ATMP, with a general description (including any drawings or pictures) and a description of active substance and constituents (including cells or tissues and their origins)
- Pharmaceutical form

- Clinical information, including therapeutic indication(s), posology and detailed instructions, contra-indications, warning and precautions, contra-interactions, effects on pregnancy/lactation/driving, and overdose (including symptoms and emergency care)
- Details on pharmacological properties and preclinical safety data
- Quality and manufacturing details, including shelf life, storage, handling, presentation, and use
- Marketing Authorization Holder information, including the marketing authorization number and date of first authorization/revision history dates

Changes to the SmPC are required if any additional new information becomes available, and these changes should be incorporated into the other related documents where appropriate. Changes cannot be implemented until approved by the originating competent authority.

Label and Package Leaflet

Labels should be present on both the immediate packaging and the outer packaging, depending on the design of the ATMP. Label requirements, as well as leaflet requirements, are listed in Annex III and Annex IV of the ATMP Directive. The package leaflet is a more robust document and contains more information derived from the SmPC whereas the label is more condensed. However, the label must indicate the specific expiry date, including the day of the month and year if known. For any ATMPs for autologous use, the label must include the unique patient identifier and the statement "For autologous use only." The label also includes the batch specific identification information for traceability. A particular challenge in the EU is the multiplicity of languages in different countries. These must be included in the labeling. An important regulatory responsibility is to assure that the translations are complete and accurate.

The leaflet contains more general information on the ATMP than the individual label, such as the different approved therapeutic indications, precautions for use, and adverse reactions. The leaflet is created for patient use, and therefore more details are required than the label, which is typically handled by a trained health care provider.

Products in European Market Landscape Through October 2018

This first ATMP was approved in Europe in 2009. ChondroCelect was reviewed through the centralized procedure and approved for marketing to adults with cartilage defects in the knee, after a 2-year review period. Since that time, only a few more products have gained market authorization. Table 1 lists the disease specific products which have been approved or are under development in different phases. The table also includes pending approvals, and ATMPs which have been discontinued.

Current Challenges and Emerging Issues

As science evolves, the ability to translate discovery into a practical application becomes more challenging. Detection systems have helped to add detail to what often have become personalized diagnoses, and these have created a need for specialized treatments that can be furnished by ATMPs. While most developers are understandably focused on the approval pathway for an ATMP, the post-marketing phase has its own challenges. Because so little is known about the long-term consequences of treatments with ATMPs, extensive additional resources must be deployed for long-term monitoring and oversight, and these add to the already high costs to develop and commercialize these medicinal products.

Changing and Demanding Regulations

The safety of patients is the most important aspect of the marketing application review. The science must be balanced with the impact to the patient, and ATMPs call for a different methodology to review a dossier. The EMA recognizes the importance of integrating a thorough review with the need for getting necessary treatments to the patients. However, many of the approved ATMPS took over 2 years from initial MAA to marketing authorization (e.g., ChondroCelect). Thus, EMA has worked to find ways to facilitate product access. Earlier initiatives include the introduction of CAT and the PRIME process to foster early discussion on products designed for unmet medical needs. In October 2017, the EMA announced a plan to encourage the development of ATMPs. Working with the European Commission Directorate General for Health and Food Safety, the EMA released 19 actions to encourage mutual understanding between Marketing Authorization holders and regulators. These actions focus on areas such as GMP and the exchange of data from related inspections, a revision of the EMA assessment procedures to foster streamlined review, and a revision to the Guideline for RMPs.

Investment and Risk Versus Benefit

The financial risk for a Marketing Authorization Holder is considerably higher when developing an ATMP than a conventional small molecule. Additional areas such as manufacturing, traceability, and long-term follow-up are areas that need to be integrated into

Table 1 List of ATMPs reviewed by the EMA or approved by the EMA (2009–18)

Product name	*Description*	*Disease*	*Authorization date*	*Status*	*Post-marketing commitments*
ChondroCelect	Viable autologous cartilage cells expanded ex vivo expressing specific marker proteins	Repair of single symptomatic cartilage defects of the femoral condyle of the knee in adults	5 October 2009	1st approved; withdrawn from market November 2016 due to financial reasons	Educational program for HCP; controlled distribution system; additional studies for safety and efficacy data
Cerepro	Concentrate for solution for injection containing sitimagene ceradenovec	To be used in combination with ganciclovir or patients with high-grade glioma	Submitted	Withdrawn August 2010 by MAH after CHMP negative opinion	Not applicable
Glybera	Viral vector expressing lipoprotein lipase	Lipoprotein lipase deficiency in adults suffering from severe or multiple pancreatitis attacks despite dietary restrictions	25 October 2012 (granted under exceptional circumstances as the condition is too rare to allow for full data package for submission)	First approved in accordance with ATMP regulation; two prior reviews with negative opinions (first submission January 2010); withdrawn by June 2016	Additional monitoring required
MACI	3rd generation autologous chondrocytes implantation	Repair of symptomatic, full-thickness cartilage defects of the knee in skeletally adult patients	June 2013	August 2014-MAH change and EMA suspended authorization	Additional monitoring required; 5-year follow-up data from primary clinical trial required; remaining biopsies to be retained by current MAH
Provenge	Autologous peripheral-blood mononuclear cells activated with prostatic acid phosphatase granulocyte-macrophage colony stimulating factor	Treatment of asymptomatic or minimally symptomatic metastatic (non-visceral) castrate resistant prostate cancer in male adult males for whom chemotherapy is not yet clinically indicated	September 2013	Production stopped in 2015 due to financial reasons; MAA withdrawn May 2015	Subject to additional monitoring
Holoclar	Ex vivo expanded autologous human corneal epithelial cells containing stem cells	Treatment of moderate to severe limbal stem cell deficiency due to physical or chemical burns in the eyes in adults	17 February 2015	On the market	Additional monitoring required
Graspa	Red blood cells as drug carriers	Oncology	Not applicable	MAH withdrew application (submitted September 2015)	Not Applicable
Imlygic	Oncolytic HSV-mediated gene therapy	Adult patients with inoperable melanoma that has spread to other parts of the body	16 December 2015	On the market	Additional monitoring required
Strimvelis	Autologous CD34+ enriched cell fraction	Treatment of patients with adenosine-deaminase-deficient severe combined immunodeficiency (ADA-SCID), who have no matching donor for a stem cell transplant	26 May 2016	On the market	Additional monitoring required
Zalmoxis	Allogeneic T cells genetically modified with a retroviral vector	Graft vs. Host disease-hematopoietic stem cell transplantation	Conditional approval 18 August 2016	On the market	Additional monitoring required

(Continued)

Table 1 List of ATMPs reviewed by the EMA or approved by the EMA (2009–18)—cont'd

Product name	*Description*	*Disease*	*Authorization date*	*Status*	*Post-marketing commitments*
Spherox (Chondrosphere)	Spheroids of human autologous matrix associated chondrocytes	Repair of symptomatic articular cartilage defects of the femoral condyle and the patella of the knee (International Cartilage Repair Society [ICRS] grade III or IV) with defect sizes up to 10 cm^2 in adults	MAA issued 10 July 2017	Submitted 3 December 2012	Training required for all healthcare providers; additional studies required
Bavencio	Human antibody specific for a protein called PD-L1	Treatment of adult patients with metastatic Merkel cell cancer	18 September 2017	Not applicable	Not applicable
Kymriah (CTL019)	CAR-T	Treatment of children/young adults with r/r B-cell ALL and adult patients with rr/DLBCL	Submitted to EMA November 2017	MAA 23 August 2018	Not applicable
Yescarta (axicabtagene ciloleucel)	Chimeric antigen receptor T cell (CAR T)	Treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma (PMBCL), high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma (transformed follicular lymphoma, or TFL	Not applicable	PRIME support; MAA 23 August 2018	Not applicable
Alofisel (darvadstrocel)	Expanded human allogeneic mesenchymal adult stem cell extracted from adipose tissue	Treatment of complex perianal fistulas in adult patients with non-active/ mildly active luminal Chron's disease	MAA issued 23 March 2018 (submitted 02 March 2016)	Orphan designation	Recommended to be administered by specialist physicians
Luxturna	Adeno-associated virus vector-based gene therapy	Treatment of inherited retinal dystrophy in adults and children caused by RPE65 gene mutations	Positive opinion from CHMP 20 September 2018	Awaiting MAA opinion	Not applicable

HCP: Healthcare provider.

pricing models. Most ATMPs have no comparable information to utilize for their pricing strategy. Obviously, they must attempt to recover the costs of development through appropriate pricing. However, since this price will be high, and treatment may be directed at a small patient population, marketplace utilization may be too low to recoup any development costs. Passing these costs onto the patients typically not feasible. Some treatments, such as Glybera, cost over 1 million Euros per patient. At the time of Glybera's market withdrawal, only one patient had been treated with the marketed product. Even though the results of treatment were successful, and the product was eventually reimbursed by health insurance, the implications of low market potential for the company were too great to outweigh the benefits. The experience with another product, Strimvelis, was similar. Strimvelis treats a disease that affects approximately 15 children per year in the EU (**Table 1**). It took 1 year to treat the first patient. At a price of more than 500,000 Euros, demand for the product could not assure the Marketing Authorization Holder of sufficient financial return. Thus, the manufacturer of Strimvelis indicated that they were divesting Strimvelis from its portfolio not long after the first patient was treated.

Other Considerations

The potential benefits associated with ATMPs create great interest in treating and curing previously untreatable disease. However, these medicinal products can create false expectations among patients, healthcare providers, and the public, who are often told by the media of miraculous findings in early stage products. Further, failures are reported in the media as stories of interest, and the subsequent skepticism about the ability to commercialize such products can affect the entire medical system. The European system of reimbursement is not harmonized across different EU member states and this can further complicate commercial considerations.

The lengthy time to market and the financial barriers to ATMPs have created an underground system of treatment without appropriate regulatory approval. Access to unregulated products may appear easier and less expensive for a patient, but those options may be ineffective or even frankly dangerous. Risks are particularly serious without the proper safety and efficacy data, and when administered by unqualified personnel.

Further Reading

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