How to commercialise ATMPs in the EU

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Abstract
Cell and gene therapy medicinal products, together with tissue engineering products (so-called advanced therapy medicinal products, ATMPs) are under active research globally. In the EU the legal and regulatory framework has been in place for a decade. However, the speed of scientific progress is challenging the available guidance and existing rulesets for ATMPs. This discrepancy has been noted by the European Commission (EC) and the European Medicines Agency (EMA), which, together, released an action plan for ATMPs in December 2017. This article addresses recent findings from the EMA PRIME scheme and provides information about procedural updates and evolving guidance in the ATMP area.

Introduction

Cell and gene therapy medicinal products, together with tissue engineering products, were brought under special legal framework of advanced therapy medicinal products (ATMPs) in 2007[1] and the scientific and technical requirements for marketing authorisation applications (MAAs) of ATMPs were adopted in 2009.[2] Several EU guidelines for these products are available,[3] yet many of them have been in use more than a decade without further revision and adaptation to meet the speed of scientific progress seen today. This discrepancy has been noted by the European Commission (EC) and the European Medicines Agency (EMA), which, together, released an action plan for ATMPs in December 2017.[4]

As part of the joint actions, the EC and EMA released a new guidance on Good Manufacturing Practice (GMP) specific for ATMPs in December 2017.[5] More recently, the EMA has released a revised version of the guideline on safety and efficacy follow-up and risk management of advanced therapy medicinal products for public consultation,[6] with the intention to reduce administrative burden in the post-marketing phase. Also, an updated version of the procedural advice on the evaluation of ATMPs[7] was published in January 2018. This document defines how the interplay between the Committee for Advanced Therapies (CAT), the Committee for Human Medicinal Products (CHMP) and the EMA should work throughout the MAA evaluation process for ATMPs. It also defines the procedure for the applicant, eg, opportunities for oral explanations (OEs) in front of the CAT and CHMP. In general the OEs are held only in front of the CAT, unless the CHMP has a particular reason for a second OE in front of the CHMP.

According to the action plan the EU is committed to supporting the development of ATMPs and aims to ensure that the regulatory framework supports – and not hinders – their development. Many of the existing ATMP guidelines are under revision and new ones are also being developed, with the guidelines for investigational ATMPs and for comparability aspects perhaps being those most awaited. Furthermore, the action plan describes that an improved regulatory framework will also contribute to promoting innovation, investments and competitiveness of the EU biotechnology sector. In this respect, few plans are shared by the EC and EMA concerning the manufacturing and use of ATMPs in the member states under so-called hospital exemption which, as a regulatory approach, has raised criticism from, and expectations for, priority actions from many industry stakeholders.[8–10]

New specific GMP guideline for ATMPs

For many years, ATMP clinical trials in the EU have mainly been conducted by academia and small-medium size enterprises (SMEs)[11] and sponsors assumed that increased flexibility has been applied when it comes to application of GMP, which was originally defined for more conventional medicines and thus considered not fully applicable for ATMPs. The new GMP guideline for ATMPs applies to both the manufacture of products for clinical trials and for commercial distribution after licensing. In general, the other available EU GMP guidelines do not apply for ATMPs after this specific guideline comes into force, unless specific reference is made thereto in the new guideline.

ATMP manufacturers are expected to comply with the new guideline no later than 22 May 2018. Interestingly, in the scope of the GMP guideline, products manufactured under hospital exemption (HE, under Article 28 of Regulation (EC) No. 1394/2007) are also mentioned, ie, it is expected that HE products are manufactured under equivalent quality standards as ATMPs with a marketing authorisation.

The new GMP guideline is built on a risk-based approach (RBA), ie, the expectations for control measures are higher when production volumes, or amount of production changes, and risks related to the manufacturing process and product itself are high. The approach is meant to bring the necessary flexibility for early clinical development and to those producing minimally manipulated cell products or few batches annually (eg, for ultra-rare indications). On the other hand, it is noted that the new GMP for ATMPs does not only bring flexibility, but also responsibilities for the manufacturers to put in place all control and mitigation measures to meet the risks of the product and of the manufacturing process. When identifying the risks, one is expected to consider the characteristics of the product and of the starting materials, level of manipulations, raw materials required for production and the overall impact of the manufacturing process on the final quality, safety and efficacy of the product.

The level of control measures (eg, the extent of in-house quality

Table 1: ATMPs with PRIME eligibility granted by the Committee for Medicinal Products for Human Use.[13]

	Name	Therapeutic area	Indication	Supporting data
1.	AAV containing factor IX gene variant (PF-06838435/SPK-9001)	Haematology - Hemostaseology	Treatment of haemophilia B	Nonclinical + Clinical exploratory
2.	AAV 5 containing a B-domain deleted variant of human coagulation factor VIII gene (BMN 270)	Haematology - Hemostaseology	Treatment of haemophilia A	Nonclinical + Clinical exploratory
3.	AAV 5 containing human factor IX gene or variant (AMT-060, AMT-061)	Haematology - Hemostaseology	Treatment of severe haemophilia B	Nonclinical + Clinical exploratory
4.	AAV 9 containing the human SMN gene (AVXS-101)	Neurology	Treatment of paediatric patients diagnosed with spinal muscular atrophy Type 1	Nonclinical + Clinical exploratory
5.	Ad 5 containing partial E1A deletion and an integrin-binding domain (DNX-2401)	Oncology	Treatment of recurrent glioblastoma in patients for which a gross total resection is not possible or advisable, or for those who refuse further surgery	Nonclinical + Clinical exploratory
6.	Allogeneic Epstein-Barr virus (EBV)-specific cytotoxic T lymphocytes (ATA129)	Haematology - Hemostaseology	Treatment of patients with EBV associated Post Transplant Lymphoproliferative Disorder in the allogeneic HSCT setting who have failed on rituximab.	Nonclinical + Clinical exploratory
7.	Autologous CD34+ haematopoietic stem cells transduced with lentiviral vector encoding the human βA-T87Q-globin gene (Lentiglobin)	Haematology - Hemostaseology	Treatment of transfusion-dependent beta-thalassaemia (also referred to as beta-thalassaemia major)	Nonclinical + Clinical exploratory
8.	Autologous CD4 and CD8 T cells transduced with lentiviral vector containing an affinity-enhanced T cell receptor to target the cancer-testis tumour antigen NY-ESO-1 (NY-ESO-1c259T)	Oncology	Treatment of HLA-A*0201, HLA-A*0205, or HLA-A*0206 allele positive patients with inoperable or metastatic synovial sarcoma who have received prior chemotherapy and whose tumour expresses the NY-ESO-1 tumour antigen	Nonclinical + Clinical exploratory
9.	Autologous CD4+ and CD8+ T cells Expressing a CD19-Specific Chimeric Antigen Receptor (JCAR017)	Oncology	Treatment of relapsed/refractory diffuse large B-cell lymphoma (DLBCL)	Nonclinical + Clinical exploratory
10.	Autologous T lymphocyte-enriched population of cells transduced with a lentiviral vector encoding a chimeric antigen receptor targeting human B cell maturation antigen with 4-1BB and CD3-zeta intracellular signalling domains (bb2121)	Oncology	Treatment of relapsed and refractory multiple myeloma patients whose prior therapy included a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody	Nonclinical + Clinical exploratory
11.	Vocimagene amiretrorepvec, nonlytic retroviral replicating vector (RRV) that delivers a yeast cytosine deaminase	Oncology	Treatment of high grade glioma	Nonclinical + Clinical exploratory
12.	AAV 8 containing the human CNGB3 gene (AAV2/8-hCARp.hCNGB3)	Ophthalmology	Treatment of achromatopsia associated with defects in CNGB3	Nonclinical + Tolerability first in man
13.	KTE-C19*	Oncology	Treatment of adult patients with diffuse large B-cell lymphoma (DLBCL) who have not responded to their prior therapy, or have had disease progression after autologous stem cell transplant (ASCT)	Nonclinical + Clinical exploratory
14.	CTL019*	Oncology	Treatment of paediatric patients with relapsed or refractory B cell acute lymphoblastic leukaemia	Nonclinical + Clinical exploratory
15.	Autologous CD3+ T Cells Expressing CD19 Chimeric Antigen Receptor (JCAR015)*	Oncology	Treatment of relapsed/refractory adult B-cell Acute Lymphoblastic Leukaemia (ALL)	Nonclinical + Clinical exploratory

** Withdrawn from the PRIME scheme.*

reviews) is determined by the volume of the manufactured products and changes introduced to the manufacturing process. In other words, more extensive and frequent reviews are expected for high volume production and when changes to the production process are made. The guidelines section on RBA gives some useful examples on how to utilise this approach.

With respect to cell products that are minimally manipulated, the GMP guideline acknowledges the increasing interest towards decentralised manufacturing through devices inside hospitals and operation rooms, yet specifies that equal validation of premises and equipment according to GMP is also expected for such production systems, even if conducted during same surgical procedure.

For early clinical studies, the GMP guideline gives freedom to the manufacturer to adapt the control strategies to the phase of development, for example, where justified, early investigational ATMP production can take place in a Class A environment with a Class C background (normally Class B background is expected). In addition, the level of control measures may be lower and specification acceptance limits wider for early phase investigational ATMPs. These, however, require agreement from competent authorities.

New additional qualification requirements are set out in the guideline for the Qualified Person (QP) who is responsible for releasing the manufactured product batches. It is specifically mentioned that this person has to have relevant expertise and knowledge of the type of ATMP and manufacturing steps for which he or she is taking responsibility. QPs, however, can also take into account their experience with manufacturing and quality control activities in small organisations with multi-skilled teams, if this can be justified.

The new GMP guideline also addresses ATMP-specific issues that are not within the scope of standard GMP, ie, issues relating to traceability and importation of cells, animal welfare for xenogeneic products, cell stock or viral seed stock requirements, process validation using surrogate materials, production, sampling and batch release issues of autologous products and decentralized manufacturing, release of products before availability of all test results, combined ATMPs, use of fully closed systems for production in Class D background (e.g. viral transduction of cells), administration of out-of-specification (OOS) products, and environmental control of genetically modified organism (GMO) products. Because most ATMPs cannot be sterilised, a lot of attention is paid to the aseptic manufacturing process and its validation. For validation of analytical tools that will be used to control the product, precise rules are given for investigational ATMPs, and these go beyond current legal and regulatory requirements.

Major obstacles in ATMP manufacturing have often concerned the early processing steps of cells and tissues and the final preparation of the product for administration (reconstitution), including the lack of standardisation therein. These steps are often performed in hospitals or corresponding tissue establishments, yet they could be considered as part of the manufacturing process (cell separation, freezing, thawing, centrifugation, etc). The guideline gives detailed instructions on how this interplay between the blood and tissue establishments, manufacturers and personnel responsible for reconstitution and administration should work. It should be noted that, where processing of cells or tissues takes place outside the actual manufacturing premises, the manufacturer remains responsible for the processing and the steps have to comply with the regulatory framework of ATMPs.

Overall, the new guideline is a comprehensive, standalone document, which takes into account the specificities of ATMPs and limitations concerning their manufacturing and quality control.

Enhanced scientific support for ATMPs

One of the key objectives of the EC and EMA joint action plan is to support ATMP developers and innovation in order to increase the opportunities for patients to be treated with novel therapies. The PRIME (PRIority MEdicines) scheme was launched in May 2016 and, since then, 166 applications have been evaluated, 42 of them being ATMPs (25.3%). According to the EMA statistics[12] published in March 2018, 21.7% of all evaluated PRIME applications were granted eligibility between May 2016 and February 2018). For ATMPs, the success rate has been higher (35.7% between May 2016 and February 2018), as can be calculated from the published EMA PRIME reports.[13] A reason for the higher success rates for ATMPs in the PRIME evaluation could be due to many ATMPs are being developed for indications that have no available treatment options. In addition, ATMPs often involve targeted therapies, for which it may be possible to demonstrate promising efficacy results earlier in the development.

From the 15 approved ATMPs, three have been withdrawn from the scheme: Juno's JCAR015 (following cessation of product development due to five deaths in the Rocket trial[14]) and chimeric antigen receptor T-cell (CAR-T) products KTE-19 and CTL019 (following the MAA submissions in 2017 by Kite Pharma/Gilead and Novartis, respectively).

The ATMPs that have been granted PRIME eligibility largely follow the main therapeutic indications, as reported for all applications.[12] However, within the non-approved products the distribution between indications is to some extent different, eg, several applications for cardiac diseases failed the evaluation and no ATMPs for this indication are receiving PRIME support at the time of publication. Other ATMP PRIME eligibility applications that were rejected between May 2016 and February 2018 (by indication) include: oncology (n=8), ophthalmology (n=4), endocrinology (n=2), haematology (n=2), neurology (n=1), gastroenterology (n=1), immunology (n=1), dermatology (n=1) and otorhinolaryngology (n=1).

Interestingly, out of the 12 active PRIME products, five are based on adeno-associated virus (AAV) vectors, which have become of high interest due to their good safety profile and new tissue specific serotypes that can be used for better targeting of the treatment. Out of the 12 active PRIME ATMPs, only one is a cell-based product (ATA129, cytotoxic T-cells for lymphoproliferative disorder). The remaining 11 products are gene therapy products for different indications (see Table 1 for list of granted PRIME ATMP products).

Sponsors who are unsuccessful in obtaining access to the EMA PRIME scheme can still benefit from the scientific advice procedure offered by the EMA. The procedural outcome is always issued in writing and such meetings offer the opportunity to discuss not only quality, safety and efficacy for a product but also post-authorisation safety studies (PASS) that may be requested during review of the marketing authorisation application. A special request for parallel scientific advice with the US Food and Drug Administration is also possible. For traditional pharmaceuticals it has been established[15] that obtaining scientific advice is linked to a better chance of regulatory approval and there are no reasons to believe that this would be any different for ATMPs. In addition to scientific advice dealing with evidence generation to fulfil future regulatory requirements for approval, it has been increasingly recognised that sponsors could benefit from advice on how best to generate evidence to support pricing and

reimbursement negotiations post authorisation. The key here is to recognise that health technology assessment (HTA) is not only focused on efficacy and safety but, in particular, evidence generated in support of relative effectiveness (ie, real-life effectiveness compared with current standard of care) and added benefit in a broad healthcare economics perspective. This may be challenging for ATMPs in particular because these products are often administered as a single or limited number of doses that fundamentally can change the course of a disease that previously could only be treated chronically (and some ATMPs may even offer a curative potential for a previously lethal condition). Moreover, HTA assessment, plus pricing and reimbursement, are all issues that are dealt with on a national basis within the EU, making a unanimous view across the EU less likely. In July 2017, the EMA launched a new procedure with associated guidance called Parallel Consultation (PC)[16]. This involves close collaboration between the EMA and EUnetHTA, the European Network for Health Technology Assessment. The new PC procedure replaces the previous parallel EMA-HTA scientific advice procedure, EUnetHTA's early dialogues and the SEED (Shaping European Early Dialogues) project for health technologies. The new procedure (PC) is a single gateway for parallel consultations with the EMA, EUnetHTA, and HTA bodies on evidence-generation plans and will also be open for ATMPs.

Procedural guidance on evaluation of ATMP MAAs

The purpose of the revised procedural advice document on evaluation of ATMPs (EMA/630043/2008)[7] is to clarify the roles of the EMA and its different committees (CAT, CHMP and the Pharmacovigilance Risk Assessment Committee [PRAC]) during the centralised evaluation of an ATMP and to define the interactions with the applicant. Specifically the document mentions that the CAT is responsible for the assessment of the ATMP applications, as well as post-authorisation activities of ATMPs. However, active interaction between CAT, CHMP and PRAC during the assessment process is expected to ensure proper flow of information. The document clarifies how divergent views of the committees will be handled and how these could be avoided, if possible. Also the roles of available EMA working parties, especially that of biologics working party (BWP), have been clarified, together with use of scientific advice groups (SAGs) or ad hoc expert groups (AEGs). As the assessment of an ATMP application involves multiple committees, the standard timetable for the centralised procedure has been adapted and presented in this document. The timelines for accelerated assessment are also different from other centrally assessed medicines, and this information is also included.

New initiatives

According to the action plan, the EC services will initiate a dialogue with national competent authorities (NCAs) to address the interplay between the GMO and the medicines legislation. This has been much awaited due to the difficulties encountered by developers when approaching first-in-man (or first-time-in-Europe) clinical studies with gene therapy products.[17] Information on the GMO procedures for investigational ATMPs in each member state is already given on the EC website.[18] Further, the guideline on investigational ATMPs is under development, with a draft guideline expected to be issued for consultation by the end of 2018. This guideline will not change the competence of NCAs to approve clinical trials but will help to create common standards for the assessment of ATMPs.

Another topic listed in the EC's action plan for ATMPs is a guidance document related to the post-authorisation follow up of efficacy and safety of these products. Regulation (EC) No 1394/2007 stipulates that applicants are required to detail in the marketing authorisation application the envisaged measures to follow the efficacy and safety, including adverse reactions to the ATMP in the post-authorisation phase. These requirements are specific for ATMPs and are additional to those requirements that follow from the pharmacovigilance legislation.

In January 2018, the EMA released a draft revised guideline on this topic for public consultation until April 2018.[19] The guideline addresses both how to identify efficacy and safety concerns with an ATMP during its development, as well as methodologies for the design of appropriate post-authorisation efficacy and safety studies. Finally, the guidance highlights the regulatory measures and financial penalties that potentially can follow non-compliance with pharmacovigilance and risk-minimisation activities.

Due to the complex characteristics of ATMPs, changes to the manufacturing process pose specific challenges, especially in terms of demonstration of comparability of the product before and after the changes. Thus, guidance on comparability testing has been awaited for several years. The new guideline should be available for consultation by middle of 2019. Several guidelines are currently under revision, eg, the overarching gene therapy guideline was expected to be adopted Q4 2017 and a draft revision of the guideline on genetically modified cells is expected for consultation by Q1 2018. Additionally the EMA promises to support SMEs and academia and improve the communication methods with all relevant stakeholders.

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