Advanced therapy medicinal products

How to commercialise ATMPs in the EU

Authors
Paula Salmikangas, Director of Biopharmaceuticals and ATMP; Steffen Thirstrup, Director; NDA Advisory Services Ltd, Leatherhead, UK.

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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 and the scientific and technical requirements for marketing authorisation applications (MAAs) of ATMPs were adopted in 2009. Several EU guidelines for these products are available, 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.

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. 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, 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’ 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.

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) 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.\textsuperscript{13}

<table>
<thead>
<tr>
<th>Name</th>
<th>Therapeutic area</th>
<th>Indication</th>
<th>Supporting data</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. AAV containing factor IX gene variant (PF-06838435/SPK-9001)</td>
<td>Haematology - Hemostaseology</td>
<td>Treatment of haemophilia B</td>
<td>Nonclinical + Clinical exploratory</td>
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<tr>
<td>2. AAV 5 containing a B-domain deleted variant of human coagulation factor VIII gene (BMN 270)</td>
<td>Haematology - Hemostaseology</td>
<td>Treatment of haemophilia A</td>
<td>Nonclinical + Clinical exploratory</td>
</tr>
<tr>
<td>3. AAV 5 containing human factor IX gene or variant (AMT-060, AMT-061)</td>
<td>Haematology - Hemostaseology</td>
<td>Treatment of severe haemophilia B</td>
<td>Nonclinical + Clinical exploratory</td>
</tr>
<tr>
<td>4. AAV 9 containing the human SMN gene (AXS-101)</td>
<td>Neurology</td>
<td>Treatment of paediatric patients diagnosed with spinal muscular atrophy Type 1</td>
<td>Nonclinical + Clinical exploratory</td>
</tr>
<tr>
<td>5. Ad 5 containing partial E6A deletion and an integrin-binding domain (DNAx-2401)</td>
<td>Oncology</td>
<td>Treatment of recurrent glioblastoma in patients for which a gross total resection is not possible or advisable, or for those who refuse further surgery</td>
<td>Nonclinical + Clinical exploratory</td>
</tr>
<tr>
<td>6. Allogeneic Epstein-Barr virus (EBV)-specific cytotoxic T lymphocytes (ATA129)</td>
<td>Haematology - Hemostaseology</td>
<td>Treatment of patients with EBV associated Post Transplant Lymphoproliferative Disorder in the allogeneic HSCT setting who have failed on rituximab.</td>
<td>Nonclinical + Clinical exploratory</td>
</tr>
<tr>
<td>7. Autologous CD34+ haematopoietic stem cells transduced with lentiviral vector encoding the human βA-TRγ2-globin gene (Lentiglobin)</td>
<td>Haematology - Hemostaseology</td>
<td>Treatment of transfusion-dependent beta-thalassaemia (also referred to as beta-thalassaemia major)</td>
<td>Nonclinical + Clinical exploratory</td>
</tr>
<tr>
<td>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-1csc)</td>
<td>Oncology</td>
<td>Treatment of relapsed/refractory diffuse large B-cell lymphoma (DLBCL)</td>
<td>Nonclinical + Clinical exploratory</td>
</tr>
<tr>
<td>9. Autologous CD4+ and CD8+ T cells Expressing a CD29-Specific Chimeric Antigen Receptor (JCAR017)</td>
<td>Oncology</td>
<td>Treatment of relapsed and refractory multiple myeloma patients whose prior therapy included a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody</td>
<td>Nonclinical + Clinical exploratory</td>
</tr>
<tr>
<td>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-IBB and CD3-zeta intracellular signalling domains (bb2121)</td>
<td>Oncology</td>
<td>Treatment of relapsed and refractory diffuse large B-cell lymphoma (DLBCL)</td>
<td>Nonclinical + Clinical exploratory</td>
</tr>
<tr>
<td>11. Vocimagene amiretrorepvec, nonlytic retroviral replicating vector (RRV) that delivers a yeast cytosine deaminase</td>
<td>Oncology</td>
<td>Treatment of high grade glioma</td>
<td>Nonclinical + Clinical exploratory</td>
</tr>
<tr>
<td>12. AAV B containing the human CNGB3 gene (AAV2/8-hCARp.hCNGB3)</td>
<td>Ophthalmology</td>
<td>Treatment of achromatopsia associated with defects in CNGB3</td>
<td>Nonclinical + Tolerability first in man</td>
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<tr>
<td>13. KTE-C19*</td>
<td>Oncology</td>
<td>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)</td>
<td>Nonclinical + Clinical exploratory</td>
</tr>
<tr>
<td>14. CTL019*</td>
<td>Oncology</td>
<td>Treatment of paediatric patients with relapsed or refractory B cell acute lymphoblastic leukaemia</td>
<td>Nonclinical + Clinical exploratory</td>
</tr>
<tr>
<td>15. Autologous CD3+ T Cells Expressing CD19 Chimeric Antigen Receptor (JCAR015)*</td>
<td>Oncology</td>
<td>Treatment of relapsed/refractory adult B-cell Acute Lymphoblastic Leukaemia (ALL)</td>
<td>Nonclinical + Clinical exploratory</td>
</tr>
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*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 manufacturing, release of products before availability of all test results, combined ATMPs, use of fully closed systems for production manufacturing, release of products before availability of all test results, combined ATMPs, use of fully closed systems for production manufacturing, release of products before availability of all test results, combined ATMPs, use of fully closed systems for production manufacturing, release of products before availability of all test results, 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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)\(^4\). 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 guideline 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.

References

Advanced therapy medicinal products


