

# Advanced Therapy Medicinal Products— an Evolving Regulatory Landscape

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*This article was developed from a presentation at RAPS Regulatory Convergence in September 2016 in San Jose, California, US. It was the opening presentation in the “Global Developments in Cell and Gene Therapy” session and covered introductory Advanced Therapy Medicinal Product (ATMP) concepts from definitions to strategic considerations and challenges currently faced by developers in this field.*

## Introduction

Broadly speaking, Advanced Therapy Medicinal Products (ATMP) in the European Union (EU) are defined by *Regulation EC 1394/2007*.<sup>{1}</sup> The overarching *EU Medicinal Products Directive, 2001/83/EC* also applies to such products.<sup>{2}</sup> Although the ATMP regulation has been in place in the EU for close to 10 years, the number of marketing authorization applications and successful approvals remains in single figures.

While many of the challenges associated with ATMP development are centered on the highly complex scientific and manufacturing aspects of such products, additional hurdles exist in relation to the lack of harmonization on ATMP definition between countries and subsequent regulatory frameworks. This is particularly true for Gene Therapy Medicinal Products (GTMP) where these products also fall within the definition of a Genetically Modified Organism (GMO).

## How are ATMPs defined?

Globally, the definition of an ATMP is viewed slightly differently by regulatory bodies. For example, in the EU, an ATMP is defined as being a Somatic Cell Therapy Medicinal Product (SCTMP), a Tissue Engineered Product (TEP), a Gene Therapy Medicinal Product (GTMP) or a combined ATMP.<sup>{3}</sup> By contrast, the US Food and Drug Administration’s (FDA’s) definition

for ATMPs is broader than the EU's description. FDA's Office of Cellular, Tissue and Gene Therapies (OCTGT) defines ATMPs as:

Cellular therapy products (that) include cellular immunotherapies and other types of both autologous and allogeneic cells for certain therapeutic indications, including adult and embryonic stem cells. Human gene therapy refers to products that introduce genetic material into a person's DNA to replace faulty or missing genetic material, thus treating a disease or abnormal medical condition.<sup>{4}</sup>

In the EU, the four subtypes of ATMPs are further defined in the following ways:

**SCTMPs** 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 of the body. They can be used to cure, diagnose or prevent disease.

**TEPs** contain cells or tissues that have been modified so they can be used to repair, regenerate or replace human tissue.

**GTMPs** contain genes that lead to a therapeutic, prophylactic or diagnostic effect. They work by inserting recombinant genes into the body to treat cancer, genetic disorders or long-term diseases.

**Combined ATMPs** contain one or more medical devices as an integral part of the medicine, such as cells embedded in a biodegradable matrix or scaffold.

## EU and US Regulatory Considerations

The regulatory environment for ATMPs is dynamic, complex and advancing rapidly. This reality requires continued regulatory intelligence to stay current, as well as frequent and early interactions with regulatory agencies to ensure collaborative discussions between clinical product development and regulatory experts. Many regulatory agencies globally encourage and provide opportunities for early interactions (starting at the stage of drug discovery), such as scientific advice in the EU with national competent authorities and/or EMA and pre-Investigational New Drug (IND) meetings in the US. However, there are different regulatory considerations and available initiatives between the US and EU; yet the overall product development concepts for an ATMP in these jurisdictions remain fundamentally the same.

For example, in the EU, one might consider seeking Committee for Advanced Therapies (CAT) classification.<sup>{5}</sup> CAT was established by EMA to offer high-level expertise to assess the quality, safety and efficacy of ATMPs. Seeking ATMP classification is an optional, no-fee procedure, but achieving such status holds significant merit in obtaining fee reductions for EMA scientific advice (currently 65 percent fee reduction from standard fees payable to EMA) and potential benefits in successfully navigating the clinical trial application process through national authorities in Europe. Other EU regulatory considerations include seeking incentives for Small-Medium Enterprises (SME), orphan designation in the case of rare diseases and hospital exemption for patient in-country hospital settings.

Developers of ATMPs also should consider if their product may be eligible for the newly introduced PRIME, which is a voluntary scheme launched by EMA in 2016 to enhance support for the development of medicines targeting an unmet medical need. It is based on enhanced interaction and early dialogue with developers of promising medicines to optimize development plans and speed up evaluation so these medicines can reach patients earlier.<sup>{6}</sup> It should be noted that more than half of the products that have been granted PRIME eligibility to date are ATMPs.

In Europe and other jurisdictions, such as Canada, there is the added complexity that certain ATMPs are also considered a GMO. A GMO is any organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating or natural recombination. Most gene therapies fall into this category. In EU countries, GMO approval must be obtained, in addition to ethics committee and competent authority approval, before a clinical trial can commence for ATMPs considered GMOs. However, the regulatory classification processes and requirements for GMO approvals are not sufficiently harmonized between EU member states, despite the *EU Deliberate*

*Release (2001/18/EC) and Contained Use (2009/41/EC) Directives* {7,8}, which results in significant challenges and timeline considerations.

In the US, regulatory product development considerations for ATMPs are quite similar in their basic concepts to those in the EU. However, there are differing processes for clinical trial approval and green light to commence the study. As of 27 April 2016, site Institutional Biosafety Committees (IBCs) and/or Institutional Review Boards (IRBs) are responsible for recommending protocols involving gene transfer to be submitted to the National Institutes for Health (NIH) for Recombinant DNA Advisory Committee (RAC) review and public consultation meeting. Notably, RAC meetings are public discussions, so a clinical trial only can start after a RAC review is completed, when RAC recommendations have been received and IRB and FDA approvals are available. The additional review by the RAC is often an extra unplanned regulatory step for developers in the field (approximately an additional four months) compared to small molecules and less complex biologicals products where a 30-day, no-objection review timeline to add a protocol to an existing IND application is all that applies.

### **Evolving Landscape for EU Clinical Trials of ATMPs**

In the EU, the new *Clinical Trials Regulation* (EU No. 536/2014) will impact clinical trials of ATMPs.<sup>{9}</sup> For all clinical trials, this new legislation will include a streamlined application process via a single entry point (the EU portal), a harmonized review and potentially, faster approval timelines. However, review timelines remain lengthier in the case of clinical trials involving an ATMP. Adding to the complexity—yet potential streamlining—of this process is that ethics committees will be involved in assessment procedures in this new regulation in accordance with the national law of the appropriate member state, but within the overall timelines defined by the regulation. In theory, these simplified submission procedures have been designed to spare sponsors from submitting broadly identical information separately to various bodies and different member states. It is currently unclear how GMO review and approval will be integrated with this new process as a harmonized assessment of this aspect is currently not foreseen in the *Clinical Trials Regulation*.

Additional changes introduced in the *Clinical Trials Regulation* include increased transparency with regard to clinical trial data as well as simplified rules for safety reporting. It will be well into 2019 before the industry sees the potential effectiveness of these efforts across the clinical trial authorization process.

Furthermore, European regulators have responded to the scientific advances in ATMPs by initiating the development of several new guidelines specific to these complex products.<sup>{10}</sup> A new EMA draft guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products was released for consultation in 2015 and is expected to be adopted in 2017.<sup>{11}</sup> The purpose of this guideline is to consolidate and update previous gene therapy guidance and provide comprehensive recommendations for developers of gene therapy products. While this guideline is aimed at products at the marketing authorization application stage, additional guidance on requirements for ATMPs in clinical trials is also under development at EMA. Finally, draft guidelines on GMP for ATMPs were released for stakeholder consultation in 2015 and 2016 by the European Commission. Taken together, these recent developments illustrate the evolving nature of the regulatory landscape for ATMPs in the EU, as well as the need for developers of these products to maintain their awareness of the most recent requirements.

### **Challenges of Emerging Market Integration**

A number of challenges exist for the emerging market integration of ATMPs. Among them are lengthy timelines for regulatory approval due to, in part, a limited number of investigative pathways and expertise, as yet, in the space. In addition, there is a “patchwork” of regulatory requirements and guidelines, as well as varying standards of care for target indications. Also, the cost of reimbursement and potential increase in clinical trials costs may need to be factored into the range of challenges.

## Is global harmonization of guidelines possible?

There are several elements that, if developed, could lay the foundation for a successful global development strategy regarding ATMPs. First, regulatory clarity in all target markets is desirable. Since not all countries have the same requirements, in-depth knowledge, surveillance and regulatory intelligence of country-specific guidelines is essential, including those guidelines being released for comment. Early, focused and continued interaction with regulatory agencies on scientific issues is a must.

Clinical development considerations also enter into global product development strategies. Harmonization could require a global “footprint” through outsourcing or partnerships. Detailed feasibility assessments that include investigator interest and familiarity, as well as the ability to handle ATMPs on a site-by-site basis would be useful, along with a good understanding of the competitor landscape. Furthermore, realistic development timelines need to take into account the potential for extended regulatory approval timelines for these products.

Finally, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) aims at bringing together regulatory authorities and pharmaceutical industry representatives to discuss scientific and technical aspects of drug registration.<sup>{12}</sup> In 2011, ICH provided training workshops on EU ATMP regulatory issues at a conference in Malaysia. There are several workshops and educational programs being introduced every year in the ATMP field and it is recommended to regularly check on news features of main agency websites for details of such activities.

## Conclusion

The regulatory environment for ATMPs is evolving and advancing, often retrospectively to product development. Thus, it is essential to have strong, continuing regulatory intelligence efforts as well as frequent interaction with regulatory agency officials. In order to ride the crest of the wave rather than have it swamp development efforts, increasing education and gaining better understanding about the nature or ATMPs—as well as how they are regulated—is imperative. This effort includes staying tuned to current EMA, FDA and global regulatory development incentives and framework as ATMP evolution continues well into the 21<sup>st</sup> century.

## References

1. *Regulation EC 1394/2007*. Legal Framework. EMA website. [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000295.jsp](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000295.jsp). Accessed 22 February 2017.
2. *EU Medicinal Products Directive, 2001/83/EC*. EMA website. [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2009/10/WC500004481.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004481.pdf). Accessed 22 February 2017.
3. Reflection Paper on Classification of Advanced Therapy Medicinal Products, EMA/CAT/600280/2010 rev.1. EMA website. [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2015/06/WC500187744.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/06/WC500187744.pdf). Accessed 23 February 2017.
4. Cellular and Gene Therapy Products. FDA website. <http://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/>. Accessed 22 February 2017.
5. Committee for Advanced Therapies (CAT). EMA website. [http://www.ema.europa.eu/ema/index.jsp?curl=pages/about\\_us/general/general\\_content\\_000266.jsp](http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000266.jsp). Accessed 22 February 2017.
6. PRIME: Priority Medicines. EMA website. [http://www.ema.europa.eu/ema/index.jsp%3Fcurl%3Dpages/regulation/general/general\\_content\\_000660.jsp%26mid%3DWc0b01ac058096f643](http://www.ema.europa.eu/ema/index.jsp%3Fcurl%3Dpages/regulation/general/general_content_000660.jsp%26mid%3DWc0b01ac058096f643). Accessed 22 February 2017.
7. *EU Deliberate Release Directive, 2001/18/EC*. [http://www.biosafety.be/GB/Dir.Eur.GB/Del.Rel./2001\\_18/2001\\_18\\_TC.html](http://www.biosafety.be/GB/Dir.Eur.GB/Del.Rel./2001_18/2001_18_TC.html). Accessed 22 February 2017.
8. *EU Contained Use Directive, 2009/41/EC*. <http://www.biosafety.be/Menu/BiosEur1.html>. Accessed 22 February 2017.
9. *Clinical Trials Regulation, EU No. 536/2014*. [http://ec.europa.eu/health/human-use/clinical-trials/regulation\\_en](http://ec.europa.eu/health/human-use/clinical-trials/regulation_en). Accessed 22 February 2017. Accessed 23 February 2017.
10. Guidelines Relevant for Advanced Therapy Medicinal Products. EMA website. [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000298.jsp&mid=Wc0b01ac05800862bd](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000298.jsp&mid=Wc0b01ac05800862bd). Accessed 22 February 2017.
11. *Guideline on the Quality, Non-Clinical and Clinical Aspects of Gene Therapy Medicinal Products. Draft*. 2015. EMA website. [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2015/05/WC500187020.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/05/WC500187020.pdf). Accessed 22 February 2017.
12. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) website. <http://www.ich.org/home.html>. Accessed 22 February 2017.

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