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Legal Update
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Europe—A Plan to Promote Advanced Therapy Medicinal Products

On Friday, October 20, 2017, the European Commission (EC) and the European Medicines Agency (EMA) published a joint action plan to promote advanced therapy medicinal products (ATMPs), the "European Commission-DG Health and Food Safety and European Medicines Agency Action Plan on ATMPs" (Action Plan).

ATMPs (gene therapy, somatic cell therapy and tissue-engineered products) are regulated as medicinal products under Regulation 1394/2007.[1] This regulation, however, does not encourage the development of ATMPs as much as had been hoped,[2] for many reasons.

Those reasons have been identified and discussed by the EC and the various stakeholders.[3] Good Manufacturing Practice (GMP) principles and rules (e.g., practices regarding batch consistency, comparability, etc.) being better adapted to the particularities of ATMPs seems to be a—if not *the*—key issue, especially for autologous products. Another issue is that EU member states transpose the European rules on tissues and cells differently in their respective national laws.[4] An additional difficulty is the application of European rules on genetically modified organisms (GMOs); many ATMPs consist of or contain a GMO, and GMO products as well as operations on or with GMOs or GMO products are subject to very stringent rules, including a prior approval regime.

The Action Plan has 19 items that cover areas from development to pricing reimbursement. (See the table that begins on page 2.) Some items have already been completed; others are ongoing or still have to be implemented. Certain issues will only start being tackled in a couple of years — the items with 2019 deadlines include the GCP (guideline on comparability) and health technology assessment (HTA) points.

Interestingly, the Action Plan indicates that the EC liaises with the member states to resolve the issue of the "hospital exemption." The hospital exemption is a derogation from the requirement to obtain a marketing authorization before placing an ATMP on the market. It was meant to be restricted to ATMPs developed by a hospital for a few of its patients. In practice, however, some member states have implemented the exemption in such a broad way that abuses occurred or could occur in a way that negatively impacts the production of ATMPs on an industrial scale. Hopefully, the EC will develop a guideline that explains the limitations to the hospital exemption, leveraging the case law of the Court of Justice of the European Union on the other exceptions to prior marketing authorization.

As more and more companies are investing in ATMPs, easing and improving the regulatory environment for ATMPs is crucial not only for Europe's competitiveness but also for the industry. Each Action Plan item is an opportunity for trade associations and companies to have their specific interests taken into account, an opportunity that should not be missed.

European Commission – EMA Action Plan

ACTION	OBJECTIVES	DEADLINE *(timelines are indicative)*
EC Guideline on GMP for ATMPs.	• To reduce administrative burden and adapt the manufacturing requirements to the specific characteristics of ATMPs. • Subsequently to the adoption of the Guideline, EMA will organise specific training to inspectors with a view to achieve more harmonisation.	Q4 2017
Exchange of information on GMP inspections within the network.	IWG meetings are being used as a platform for exchange of information and experience on the application of GMP to ATMPs.	Ongoing
The European Commission services will initiate a dialogue with national competent authorities to address the interplay between the GMO and the medicines legislation.	• To reduce discrepancies across the EU regarding the application of GMO rules (Directives on deliberate release or contained use) to ATMPs containing or consisting of GMOs. • Issues relevant for both clinical trials and marketing authorisation will be addressed. • The aim is to help create coherent approaches for the assessment of these novel products without changing the basic legislation.	Q3 2018
Revision of EMA procedures regarding the assessment of ATMPs.	To reduce administrative burden, avoid overlaps between the tasks of the various committees involved, and address the specific needs of ATMP developers (e.g. longer clock stops).	Q4 2017
Provide enhanced scientific support for the development of ATMPs.	• Increased opportunities for early dialogue with multidisciplinary or multi-stakeholder expert teams. • Streamlined EMA procedures for scientific advice, incl. strengthened interaction between EMA committees.	Ongoing PRIME Parallel EMA-HTA SA
EMA Guideline on Investigational ATMPs.	• To avoid discrepancies across the EU regarding the requirements for ATMPs in the clinical trial phase. • The Guideline will not change the competence of Member States to approve clinical trials but it will help create common standards for the assessment of these novel products.	Draft guideline for consultation - Q4 2018

EMA Scientific Guidelines on ATMPs.	• The adoption of the guideline on gene therapy and the review of the guideline on genetically modified cells will support developers of these novel therapies by clarifying regulatory expectations. • The development of guidance on comparability will also address the questions commonly confronted by ATMP developers.	Gene therapy guideline - adoption expected Q4 2017 Draft revision of Guideline on genetically modified cells - consultation Q1 2018 Guidance on comparability - Q2 2019
GLP for ATMPs: development of adapted guidance.	To facilitate the approval of clinical trials/granting of marketing authorisation in cases where GLP compliant preclinical studies are not feasible.	Q2 2017 Published: -Marketing authorisation here - Clinical trials here
Revision of the EMA Guideline on Safety and Efficacy and Risk Management Plans for ATMPs.	To reduce administrative burden in the post-marketing phase.	Q2 2018
The EC services to initiate a reflection process with the Member States on the hospital exemption.	To discuss with Member States the current situation and address possible options.	Continuous process
EMA Q&A on the application of the risk based approach for ATMPs that have not been subject to substantial manipulation.	To explain to developers the possibilities afforded by the risk-based approach (flexibility, reduction of certain requirements for the submission of a marketing authorisation application depending on specific risks).	Q1 2017 Published here
GCP for ATMPs.	To address as appropriate any specific needs to ATMP developers.	2019
Scientific considerations on gene editing technologies.	To reflect on emerging techniques on gene editing.	Q2 2018
Awareness and training of the network.	Awareness sessions for the EU network on ATMP-related topics (e.g. AAV Vectors, genome editing); expert meetings organized by CAT	Continuous process

Increased stakeholder support: SMEs	Publication of a specific action plan for SMEs.	Q2/2017 Published here
Increased stakeholder support: Academia	Publication of an action plan specifically designed on the framework of collaboration with academia.	Q1 2017 Published here
Increased stakeholder support: ATMP-topic specific	Update the ATMP dedicated webpage on EMA's website to act as a central resource of relevant information.	Q4 2018 See EMA webpage here
Increase awareness of stakeholders on EU regulatory processes and framework.	Development of targeted communication/training material in particular for small developers, academia and stakeholders supporting ATMP development; participation at workshops and relevant fora.	Ongoing
Interaction with EUnetHTA	Foster increased interaction between EMA and EUnetHTA on ATMPs to increase understanding of health technology assessment, regulatory processes and clinical added value of ATMPs.	Joined training / workshop planned in 2019

For more information about the topics raised in this Legal Update, please contact the following lawyer.

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Endnotes

1 Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004.

2 http://www.ema.europa.eu/docs/en_GB/document_library/Report/2016/06/WC500208080.pdf

3 http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/02/WC500220952.pdf

4 ATMPs typically originate from cells, and the processing of cells (donation, procurement, testing, distribution, etc.) is subject to national law.