Commentary: Tatiana Reimer and Paula Salmikangas

Strengths and shortcomings of new EU rules for ATMPs

The EU pharmaceutical legislation consisting of Directive 2001/83 and Regulation 726/2004 was originally created to guarantee quality, safety and efficacy of medicines in the EU, but also to generate a centralised marketing authorisation procedure whereby medicines could get licensed in all member states with one single application. In addition, it consists of measures to support innovation and competitiveness.

For Advanced Therapy Medicinal Products (ATMPs), which include cell and gene therapies and tissue engineered products, a lex specialis, Regulation 1394/2007/EC, came into force in 2009. Under this Regulation, a Committee for Advanced Therapies (CAT) was established to review and recommend decisions on the authorisation of ATMPs. Technical requirements for authorisation were later established with the implementation of Directive 2009/120/EC.

The legislative proposal published by the European Commission (EC) on 26 April 2023 is composed of two legal documents: a new Regulation replacing Regulation 726/2004/EC and a new Directive replacing Directive 2001/83/EC. The revised framework is meant to introduce a new pharmaceutical strategy to the EU, under which unmet medical needs can be addressed, administration reduced, and innovation be promoted across the union. The proposal contains several provisions that are applicable to all medicinal products, but also some ATMP-centric revisions.

In this article, the legislation's strengths and shortcomings for ATMPs are discussed keeping in mind that the proposal still needs to be approved by the European Parliament and Council of Ministers.

Perhaps the most ground-breaking feature of the legislation is a proposal to abolish three committees at the European Medicines Agency: the Committee for Advanced Therapies (CAT), the Paediatric Committee (PDCO), and the Committee for Orphan Medicinal Products (COMP). Significantly, each of these committees is composed of experts in their respective fields: cell and gene therapies and tissue-engineered products; medicines for children; and products for rare diseases.

Instead, decisions traditionally taken by these committees would move to the Committee for Medicinal Products for Human Use (CHMP). In the recitals of the legal documents, it is mentioned that these committees would be changed into working parties (WP), however, the setup of such working parties and their future roles are not addressed in the binding legal text. This would apparently mean an expansion of the CHMP's work to cover not only new chemical entities (NCEs) and biological drugs, but also ATMPs and all the specific procedures for orphan and paediatric medicines.

This would also mean a transition of the ATMP marketing authorisation application (MAA) rapporteurships from CAT members to the CHMP members, including ATMP classification and environmental risk assessment reviews.

The legislative proposal acknowledges that in such cases the competence of the CHMP for these different tasks and product types must be ensured, suggesting that the current composition of the CHMP will need to be revised as well.

Members of the CAT have always been nominated to serve the committee on the basis of their expertise in relevant ATMP areas. Furthermore, CAT has also included external members e.g., physicians or patient representatives specialised in ATMPs. It remains unclear how the expertise and knowhow of the CAT established during the last 14 years, would be maintained in the CHMP. Only a few of the members of the CHMP, who have also been members of the CAT, have acted as rapporteurs for ATMPs.

At the same time the proposal would lower the MAA review time from 210 days to 180 days, which would further increase the burden on the CHMP. From the proposal it remains unclear how the ATMP expertise is to be maintained and how all the work of the three committees would be included in the CHMP.

Considering all of these issues together, one cannot ignore a worst-case scenario where a lot of the expertise of the CAT and knowhow is lost, leading to difficulties in assessments, failures to meet deadlines and longer lists of questions from the CHMP. Of special concern in this scenario are new, first-in-class ATMPs, many of which are in clinical development for various indications and don´t have any regulatory precedent.

By comparison, the US Food and Drug Administration (FDA) has addressed the future challenges of the growing numbers of ATMP applications and their novel complex technologies by setting up a new super office, OTP (Office for Therapeutic Products), for cell/tissue and gene therapy products. The FDA is also increasing the capacity of OTP and continuously improving its processes.

The Hospital Exemption

In the proposed new Directive, the Hospital Exemption (HE) has been formalised with some defined rules for the control of its use in the member states. Member states would not only be required to approve the HE procedures but safety and efficacy data from the HE use would also be collected systematically and reported to the EMA. There are no limits for the manufacturing volumes, but the products manufactured under HE should comply with the principles of the good manufacturing practice established for ATMPs, traceability should comply with Regulation 1394/2007/EC and pharmacovigilance requirements are expected to be equivalent to those provided for at EU level.

On the other hand, the legislation appears to omit any requirement for transparency of HE procedures as their outcomes are not required to be publicly available. This is in sharp contrast with EMA transparency rules, e.g., openness in communicating the outcomes of marketing authorisation procedures.

The current rules of HE have led to an unusual hospital exemption procedure in Spain[1] where a CD19 directed chimeric antigen receptor (CAR) T cell product received authorisation in early 2021 from the Spanish Agency of Medicines and Medical Devices to treat adults with relapsed/refractory acute lymphoblastic leukaemia. One may ask what the legal foundation for such a practice is when similar products are already authorised and commercially available in the EU?

The use of HE is said to lower prices, but these products are often based on already existing products, whereby the development costs are not the same as for first-in-class ATMPs. In addition, it is unclear how the prices of HE products could be lowered in case the same requirements for quality, safety and efficacy are expected as for centrally authorised ATMPs.

Biosimilar ATMPs

Article 2 (6) of the new Regulation expands the definition of "similar active substance" to ATMPs, for which "the principal molecular structural features cannot be fully defined." In such cases, the similarity between two active substances shall be assessed on the basis of the biological and functional characteristics.

Considering how complex many ATMPs are, each requiring a unique manufacturing process and quality control systems, it remains unclear whether the concept of ´biosimilar ATMPs´ is viable and worth going for with extensive analytical comparability programmes. Nontheless, for more simple products with limited parameters (e.g. AAVs, mRNAs), provisions set for biosimilar ATMPs in the new legislation and the proposal to lower the data protection time of authorised products could lead to use of the biosimilar route and increased competition within the industry.

A primary objective of the proposed legislation is to increase patient access to new medicinal products with affordable prices. While reducing the standard data protection period to six years from eight, the proposal also gives companies four ways in which to recover some or all of this time. One of these measures would be to launch a new product across all EU member states rather than in just a few countries. This would be very challenging for small companies developing novel ATMPs. Product launches in the EU follow a country's decision on whether or not to reimburse a new pharmaceutical product. Some countries take longer than others to reach a decision, and not all EU countries have the same financial resources to support full reimbursement.

Achieving full distribution for ATMPs across the EU therefore may not be easy. Many ATMPs are produced at a scale that is too small to generate enough product to cover the entire EU market.

Other issues that are relevant for ATMPs and are addressed in the new proposal include rules for qualified persons (QPs), decentralised manufacturing (where production occurs in multiple locations), and the possibility that quality master files could be used in the EU. Currently US Drug Master Files (DMFs) for starting and raw materials like viral vectors, DNA/RNA molecules, complete media containing cytokines and growth factors, are not accepted for clinical trial applications (CTA) or for marketing authorisation applications (MAAs). Before the start of the new CTA submission system in the EU, some member states accepted that vendors could provide the information on such materials directly to the reviewing authority. With the new clinical trial information system (CTIS) in place, this is no longer feasible, as all information going through the CTIS will be visible to the applicant. Therefore the establishment of quality master files would be a good solution to allow a reference of confidential information in regulatory submissions.

A positive aspect of the legislation is a clear improvement of the Environmental Risk Assessment (ERA) procedure for genetically modified organisms (GMO). Currently, member states have been using two alternative legal frameworks for the GMOs, either 'deliberate release´ or ´contained use,´ for which the processes and regulatory frameworks differ.

According to the proposal, regulation of GMO/ATMPs will be based solely on the deliberate release framework (Directive 2001/18/EC), the process is simplified for CTAs and MAAs and a public registry for the ERA studies will be generated. For non-clinical development, in line with the 3R principles, the proposal is asking that in vivo non-clinical studies should be justified.

As a new element in the legal framework, a concept of a "Regulatory Sandbox" is included. This should allow the testing of new regulatory approaches for novel products under real world conditions. The European Commission and the EMA will scan for promising new developments, that could benefit from such a regulatory framework, simultaneously ensuring that the approach does not distort the market for innovative medicinal products.

Reference:

1. Trias, E., Juan, M., Urbano-Ispizua, A. and Calvo, G. The hospital exemption pathway for the approval of advanced therapy medicinal products: an underused opportunity? The case of the CAR-T ARI-0001. *Bone Marrow Transplantation* (2022); 57:156–159.

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