Why Regulatory Convergence is Key to Global Development of Cell and Gene Therapies

There is growing excitement about the potential shown by cell and gene therapies, particularly in rare diseases. First, though, these therapies face challenges both in development and in aligning to regulatory guidance that was established long before the advent of advanced therapeutic medicinal products (ATMPs). Francesco Lanucara of PharmaLex explores the challenge of navigating guidelines that don't always reflect the complexity of ATMPs and the importance of achieving regulatory convergence across different regions.

There have been significant advances in the field of cell and gene therapy in recent years with the approval of a growing number of therapies that target rare diseases. As knowledge is continuously gained on key aspects of the manufacturing processes and the quality attributes of cell and gene therapy products, regulatory guidance also continues to evolve.

Both the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) have been busy in the past few years publishing new guidance for advanced therapeutic medicinal products (ATMPs). For example, the FDA produced two new guidances this year – one on CAR T cell products[1] and one focused on products incorporating genome editing (GE) of human somatic cells.[2]

Largely, though, developers have had to find ways to work with long-established ICH guidelines that were designed with more conventional biotechnological products in mind, such as monoclonal antibodies. Due to the complexity of ATMPs, the regulatory framework has evolved differently in various jurisdictions, as is reflected by the diverse approaches from EMA and FDA to aspects of the development process, particularly with regards to implementation of GMP compliance and the definition of starting materials.

The evaluation and regulation of cell and gene therapy products would benefit from greater convergence and harmonisation of requirements and standards across different regions, supported by collaboration between industry, non-profit, academic and other organisations, and regulatory authorities.

Why ICH Harmonisation Guidelines Need an ATMP Update

The ICH was established more than 30 years ago as a global platform for harmonisation of technical guidelines and requirements for the development and registration of pharmaceutical products. Today ICH has 20 members and 35 observers, and many health authorities worldwide now apply ICH guidelines to their regulatory framework. Some countries take ICH guidelines that don't easily fit to the complexity of ATMP medicines, resulting in developers of ATMPs struggling to meet expectations during the evaluation of their submissions.

While ICH has developed some guidelines relevant to gene therapies, for example, guidance on nonclinical biodistribution studies in the development of gene therapies,[3] many activities covered by well-established ICH guidelines don't easily apply to cell and gene therapies. There is, therefore, a need for guidance to be updated to take into consideration the variety, complexity and challenges of cell and gene therapies.

As an example, requirements for batch release testing cannot be applied in the same way to cell-based products as they are to an antibody. Typically, with cell-based products, tissue is taken from the patient, which is then genetically modified and returned to the patient. Cell-based products are often characterised by short shelf-lives, challenging the execution of traditional release testing, such as sterility, in a time frame that allows delivery of the product to the patient without compromising the product quality.

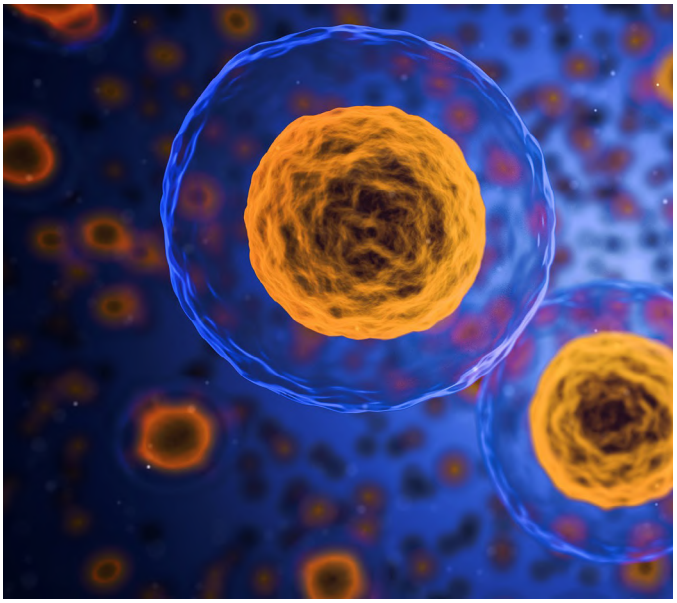
The challenges associated with ATMPs are recognised by schemes such as EMA's PRIME programme, which provides developers of innovative ATMPs with options to adapt their CMC (chemistry, manufacturing and controls) development to the restricted timelines that are typically faced in the approval of these products. As an example, alternatives to the standard process qualification and validation as described in the ICH are described for ATMP programmes, where the number of batches manufactured at the time of submission of Marketing Authorisation Application may be limited.

While the flexibility provided by schemes such as PRIME is welcome, harmonised ICH guidance to support ATMPs that can't go through standard development processes would be preferable since this would ensure a smoother process across all regulatory authorities.

Dealing with Conflicting Requirements from Agencies

The pathways for ATMP developers are also made more difficult by differences in what regulators in Europe and the US require to assess clinical trial applications (CTAs). Drug developers typically outsource production to contract development and manufacturing companies (CDMOs) who often restrict proprietary information on the manufacturing process to Drug Master Files (DMFs) or Regulatory Support Files (RSFs) which are submitted to the agency for evaluation but are not visible to the sponsor.

The new Clinical Trial Regulation (CTR), which came into effect in the EU on 31 January 2022, does not include the option to submit a separate supporting file (similar to a DMF or RSF) for investigational medicinal products as part of the Investigational Medicinal Product Dossier (IMPD).



Additionally, Annex VI of the new CTR states specific labelling requirements for IMPs, including labelling of the expiry date on the immediate packaging, which challenges the practicality of updating expiry dates for those packaging configurations designed to store the product in frozen conditions, such as the cryobags typically used for cell-based ATMPs. This requirement is a further issue for sponsors who initiated clinical trials in jurisdictions outside the EU and are now having to redevelop their labelling to comply the Annex VI.

While the introduction of the CTR poses some issues, the new regulation does bring harmonisation to CTA evaluations. Previously, the clinical trial evaluation was country-specific in Europe, which meant companies had to deal with different expectations with their ATMP trial applications. With the CTR, the application will be reviewed by one body, representing many countries, and applicants will receive one EU-based opinion, rather than many national opinions. This is expected to speed up clinical trial approvals.

A Drive Towards Mutual Recognition for ATMPs

ATMPs face another hurdle that other regulated products do not: mutual recognition. The EU has mutual recognition agreements with many other authorities for conformity assessment, which, among other things, allows authorities to waive batch testing of products imported into their territories.[4] This agreement does not extend to ATMPs, which means sponsors must retest batches in the EU before their cell or gene therapy can be released in the EU by the qualified person (QP).

There have been exceptions with cell and gene therapies where companies were able to justify not retesting based on the limited amount of material, as was the case for Luxturna[5] and Zolgensma.[6] While the European public assessment reports for both products noted that the mutual recognition agreement for GMP between the US and EU or UK does not apply to ATMPs, GMP guidelines do allow some flexibility for release testing due to the small batch size of these orphan products.

As the authors of a June 2021 paper in Molecular Therapy noted,[7] regulatory reliance and work sharing between regions – where regulators in one region use assessments performed by regulators in another region to inform their decision-making – could be of particular value for gene therapies, whose complexity could strain the infrastructure of smaller regulatory agencies. "For example, approval of a gene therapy product by the FDA or EMA could form the basis for approval in other countries, leveraging the dossiers used to support initial approval," the authors wrote.

There are efforts underway to better standardise and harmonise processes and improve industry-regulatory collaboration. For example, the FDA has joined a public-private consortium, the Bespoke Gene Therapy Consortium (BGTC) which is part of the Accelerating Medicines Partnership program.[8] The goal is to build platforms and standards to speed the development and delivery of gene therapies. More such efforts are needed to achieve the objective of bringing innovative, life-changing gene and cell therapies to patients.

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