REGULATORY FOCUS

Advanced therapies: Navigation and application of EU and US guidelines during product development

By Kirsten Messmer, PhD, RAC, and Richard Dennett, PhD

Continued progression and understanding in the development of advanced therapies has led to a significant increase in the number of products and types of indication under investigation, particularly for treating serious and life-threatening conditions. Although the principle regulatory requirements and guidance, as issued for traditional biologic products, can be generally applied, advanced therapies require additional regulatory and strategic considerations because of their specific novelty and greater complexity of parts. This article provides a high-level overview and navigation guide through the multitude of available advanced therapy guidance in the EU and US.

Introduction

Advanced therapies have gained increasing attention over recent years by offering a new and inventive angle of attack to treating an array of medical conditions. Although all drug products share a common development backbone, the specific nature and design of cell and gene therapy (CGT) products have a greater degree of complexity compared with traditional pharmaceutical and biological drug products, therefore requiring additional strategic considerations.

Those more complex elements have been addressed in a companion article titled, "Advanced therapies: 'Trip hazards' on the development pathway."[1]

The evolution of CGT products has necessitated a parallel maturation of regulatory frameworks and guidelines. This has led to the growth of a strong library of comprehensive, clear, and accessible development information provided by regulatory authorities. However, there are some regional differences in guidances, leading advanced therapy developers to carefully examine the starting point and how to best fit their strategic development plans. The volume of available guidelines may also create a sense of information overload among biotech developers in the field, leading them to wonder exactly where they should begin the process.

This summary article takes a high-level, comparative look at EU and US guidances for advanced therapy, highlighting main points of consideration and providing general strategic mapping and signposting of how best to orchestrate their respective use during the course of product development for the EU and the US. The article is geared toward early stage biotech companies, but also should act as a quick memory aide for more experienced and larger companies. Only a snapshot of some of the key guidance is provided. The reader is directed to the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) websites for further guidance and related information.[2-5]

Some general points of comprehension:

- **Nomenclature**
  - Gene therapy, somatic cell therapy, and tissue-engineered medicines in the EU are referred to as advanced therapy medicinal products (ATMPs).
  - In the US, the comparative tags are cell and gene therapy products and regenerative medicine advanced therapies.
  - In effect, these terms broadly correspond with one another. However, there are slight differences in the pathways of tissue regulation in the US. The terminology of advanced therapy and cell and gene therapy products is becoming more interchangeable.
  - The term "advanced therapies" will be used in the remainder of this article to include all previously mentioned product types.

- **Regulatory bodies**
  - In the EU, advanced therapies are regulated by the EMA, with a scientific assessment by the Committee of Advanced Therapies (CAT) within the EMA, linking to the quality, safety and efficacy of the advanced therapy medicine. The CAT provides assessment feedback to the Committee for Medicinal Products for Human Use (CHMP). The CHMP makes the approval or denial recommendations to the European Commission. Advanced therapy medicines are authorized centrally through a single evaluation and authorization procedure.
  - In the US, the regulation of advanced therapies is overseen by the Center for Biologics Evaluation and Research's (CBER's)

Office of Tissues and Advanced Therapies, with the review of policies and product application data relating to the safety, effectiveness, and appropriate use by the Cellular, Tissue and Gene Therapies Advisory Committee, as needed by the agency.

- **Strategy tip**
  Most advanced therapy developers may initially target only one market, which will require conforming to either EU or US guidance. However, depending on the initial territory – marketing authorization application (MAA) for the EU, or investigational new drug (IND) and biologics license application (BLA) for the US – it is highly useful to explore the content and context of both sets of guidance to acquire a more complete understanding of regulatory requirements. Conforming with requirements in both jurisdictions from the beginning will later save time and money for expansion of the target markets.

- **Main portals and guidelines**
  - European Union
    - Advanced therapy medicinal products: Overview[2]
    - Guidelines relevant for advanced therapy medicinal products[3]
  - United States
    - Cellular and gene therapy products[4]
    - Cellular and gene therapy guidances[5]

- **How to use this article**
  The article is divided into development stages (Stage 0/Pre-IND, phases I-III, and end of phase II/phase III to marketing authorization) and provides key guidances and considerations at each of these stages. The reader should consider these to be highlights and further seek out the respective and applicable guidances. It is of utmost importance to read the guidances in full and follow their recommendation to ensure a regulatory-compliant advanced therapy development program.

Stage 0/pre-IND

At the start of any development program, it is pertinent to determine exactly what the product is and what the target product profile might be: Is the advanced therapy a cell or gene therapy, both, combined with a medical device, or possibly so innovative that it might not yet be classified as either?

For some products, the developer might clearly determine that it is a cell or gene product, but sometimes the boundary might be less clear, for example, in terms of ex vivo gene-transduced cell product or cellular products with minimal manipulation. To support the understanding and determination of the advanced therapy product type, the EMA offers formal evaluation or classification, including a helpful classification listing of CGT products that provides clear examples the help in determining where a product might best fit.[6]

The EMA and FDA also maintain listings of approved products that can be used to determine the product type.

As a first step or starting point for understanding the regulatory requirements and available guidance documents for advanced therapies, the EU has a set of "overarching" guidelines, which are highlighted in green in **Table 1** (pp. 5-6). These are essentially broad "parent guidelines" that spell out the main framework of the regulatory and development requirements for advanced therapies to take a product through to prospective license approval. These overarching guidances are supported by an in-depth set of more focused and product-specific guidelines.

The FDA has a similar set of baseline guidance documents covering the framework and factors necessary for nonclinical chemistry, manufacture, and controls (CMC) plus clinical considerations and requirements.

Table 1 provides a selected cross-section of principle guidance, including the overarching guidances noted. The reader should consult the respective regulatory agency websites for a more extensive guideline listing.

Front-end synopsis and building of understanding

Overall, the full development content of the EU and US guidances is very similar and provides logical title content for the various requirements. It should be reiterated here that the two guidelines highlighted below and taken from Table 1 are of particular value for early stage companies developing investigational products:

- **EU –** Guideline on quality, nonclinical, and clinical requirements for investigational advanced therapy medicinal products in clinical trials.[9]
- **US –** Chemistry, manufacturing, and control information for human gene therapy investigational new drug applications.[10]

Early stage regulatory advice is also extremely beneficial in discussing the scientific nuances and clinical value of these products and the proposed development pathway. Both the EMA and FDA offer opportunities to seek advice as early as at the proof-of-concept stage. The EU Innovation Task Force offers early stage consultations, while, in the US, the FDA conducts INTERACT (INitial Targeted Engagement for Regulatory Advice on CBER producTs) meetings that offer consultation even before the pre-IND stage. However, more realistically, better advice can be provided at a more progressive stage of development and when an investigational product dossier is under development through EU scientific advice or US pre-IND meetings. Regulators have consistently encouraged advanced therapy developers to seek advice early.

TABLE 1 Cross-section of key guidelines for advanced therapies in the EU and US

Guideline
European Union
Gene therapy medicinal products[7]
[a]The overarching guideline for human gene therapy medicinal products is the guideline on the quality, nonclinical, and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014)
[a]Guideline on quality, nonclinical, and clinical requirements for investigational advanced therapy medicinal products in clinical trials
Guideline on safety and efficacy follow-up and risk management of advanced therapy medicinal products
Quality, preclinical, and clinical aspects of gene therapy medicinal products
Quality, nonclinical, and clinical aspects of medicinal products containing genetically modified cells
Development and manufacture of lentiviral vectors
Nonclinical studies required before first clinical use of gene therapy medicinal products
Nonclinical testing for inadvertent germline transmission of gene transfer vectors
Risk-based approach according to Annex I, part IV of Directive 2001/83/EC applied to advanced therapy medicinal products
Follow-up of patients administered with gene therapy medicinal products
Scientific requirements for the environmental risk assessment of gene therapy medicinal products
Cell therapy and tissue engineering[8]
[a]The overarching guideline for human cell-based medicinal products is the guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006)
[a]Guideline on quality, nonclinical, and clinical requirements for investigational advanced therapy medicinal products in clinical trials
Guideline on safety and efficacy follow-up and risk management of advanced therapy medicinal products
Potency testing of cell-based immunotherapy medicinal products for the treatment of cancer
Risk-based approach according to Annex I, part IV of Directive 2001/83/EC applied to advanced therapy medicinal products
Xenogeneic cell-based medicinal products

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TABLE 1 (continued)

Guideline
United States[5]
Nonclinical
Preclinical assessment of investigational cellular and gene therapy products
CMC
[a]Chemistry, manufacturing, and control information for human gene therapy investigational new drug applications
Guidance for human somatic cell therapy and gene therapy
Regulatory considerations for human cells, tissues, and cellular and tissue-based products: Minimal manipulation and homologous use
Determining the need for and content of environmental assessments for gene therapies, vectored vaccines, and related recombinant viral or microbial products
Eligibility determination for donors of human cells, tissues, and cellular and tissue-based products
Clinical
[a]Considerations for the design of early phase clinical trials of cellular and gene therapy products
Long-term follow-up after administration of human gene therapy products
Medical device
Evaluation of devices used with regenerative medicine advanced therapies

[a]The "overarching" guidelines spell out the main framework of the regulatory and development requirements for advanced therapies to take a product through to prospective license approval.

Since most advanced therapies treat rare and/or life-threatening diseases, programs to expedite the development and/or assessment should be considered. There are several programs – such as orphan drug designation, fast track, or accelerated assessment/approvals – available for all products, including small molecules and biologics. However, applications also can be made for programs geared more specifically to advanced therapies – such as the EU's PRIority MEdicine (PRIME)/accelerated assessment route or the US's regenerative medicine advanced therapy (RMAT) designation – based on the clinical potential of the product and whether it addresses an unmet medical need:

- **EU –** PRIME/other routes include accelerated assessment and authorization under exceptional circumstances.[11]
- **FDA –** RMAT (Expedited Programs for Regenerative Medicine Therapies for Serious Conditions)/other routes to consider include fast track, breakthrough therapy, priority review and accelerated approval.[12]

The transition from nonclinical to phase I/first-in-human is an important stage. The nonclinical study program and product CMC have to support the safety of initial human clinical studies. The manufacture of the investigational product needs to be representative of the product to be used at later clinical stages and the product, including product-critical quality attributes, has to be

demonstrated to be comparable. In addition, the biological activity also needs to interrelate. It is important to make sure this fundamental stage is properly covered and to not let any time pressures place undue force on this.

When addressing product-specific complexity, the principle issue of advanced therapy products is that there is not only the diversity of types of products, such as cell, gene, and tissue products, but that each product type has a different array of considerations, such as the availability of animal models, product characterization, autologous/allogeneic manufacturing routes, stability, and logistics.

In addition, advanced therapies have a wider range of risk factors: genetic risk factors, immunogenicity, and interhuman genetic variability. These scenarios need to be derived, controlled, and addressed across CMC and clinical development programs and may need to be addressed differently with different diseases or disorders.

This has led to the generation of advanced therapy and/or disease-specific guidelines discussing the regulatory agencies' expectations (**Table 2**). Most of these guidances were generated reactively to the need to provide guidelines for products under development for specific indications (e.g., knee cartilage repair, hemophilia).

TABLE 2 Regulatory guidance specific to products and/or advanced therapies for specific indications

Guidance
European Union
Reflection papers[3]
Clinical aspects related to tissue-engineered products
In vitro cultured chondrocyte containing products for cartilage repair of the knee
Stem cell-based medicinal products
Questions and answers on comparability considerations for advanced therapy medicinal products
United States[5]
Cellular therapy for cardiac disease
Considerations for allogeneic pancreatic islet cell products
Preparation of [investigational device exemptions] and [investigational new drugs] for products intended to repair or replace knee cartilage
Human gene therapy for rare disease
Human gene therapy for hemophilia
Human gene therapy for retinal disorders

Good practice requirements for advanced therapies

Bench scale development through to good manufacturing practice (GMP) in the manufacture of a clinical product is a special point of consideration for smaller and/or academic advanced therapy developers. Some universities and hospitals may have the benefit of early stage GMP-capable production units, but not necessarily for the full-fledged supporting facilities, layouts, and operations or for scaling up or scaling out production as the clinical development program matures. Some of these institutions may have implemented International Organization for Standardization (ISO) standards at best. These units are often found in product manufacture of ex vivo gene-manipulated autologous cell products where cells are taken from the patient, transduced, and then re-infused into the patient or cell/tissue-based products.

The European Commission has recognized and bridged this GMP intermediary situation by developing a GMP guideline specifically for early stage developers of advanced therapies in biotech and in university and hospital environments. This guidance adapts the EU GMP requirements to the specific characteristics of advanced therapies and addresses the novel and complex manufacturing scenarios used for these products, as well as imparting a risk-based approach to the manufacture and testing. The US has a GMP guideline for broader investigational products in phase I development:

- **EU –** EudraLex Volume 4: The Rules Governing Medicinal Products in the European Union – Good Manufacturing Practice: Guideline on Good Manufacturing Practice Specific to Advanced Therapy Medicinal Products[13]
- **US –** Current Good Manufacturing Practice for Phase 1 Investigational Drugs[14]
- **Additional guidance –** Q7 Good Manufacturing Practice for Active Pharmaceutical Ingredients.[15] (Table 1 in this guidance titled, Application of this Guidance to API Manufacturing, shows where the GMP boundary between source and manipulated material should occur).

Similarly, there are additional guidelines or updated documents for good laboratory practices (GLP) and good clinical practices (GCP) for advanced therapies:

- **EU –** Eudralex Volume 10, chapter 5: Guideline on Good Clinical Practice Specific to Advanced Therapy Medicinal Products.[16]
- **CAT (with EC and Clinical Trial Facilitation Group) –** Good laboratory practice (GLP) principles in relation to ATMPs. (A question-and-answer document on GLP principles to be taken into account in relation to advanced therapies).[17]

Ongoing phases I-III development

It is important to remember that advanced therapies are still biologics. Therefore, although the aforementioned guidelines for advanced therapies should readily support development of these product classes through phases I-III, they should be read and applied in conjunction with guidelines for

conventional biologics and those from pharmacopeia and the International Council for Harmonisation (ICH; **Table 3**).

In addition, advanced therapies are more complex than conventional therapies and may therefore need a higher number of validation batches as well as adequate supporting data. It is imperative to allow sufficient time for the generation of acceptable batch data. For any product, this needs to be backed by a watertight development package that frames a safe, quality-driven, and efficacious product. The data package also needs to confirm that the commercial process and product is robust and reproducible.

Emerging guidance

The regulatory landscape is constantly changing and adapting to new experience and knowledge gained for all pharmaceutical products. However, advanced therapies are a particularly rapidly evolving field. Global regulators have taken note and are committed to releasing timely guidance for an ever-increasing diversity of advanced therapies.

TABLE 3 Examples of additional guidance for biologics and advanced therapies, including monographs and chapters from the International Council for Harmonisation and pharmacopeia[a]

Guidance
European Union[3]
Development and manufacture of lentiviral vectors
Gene therapy product quality aspects in the production of vectors and genetically modified somatic cells
Potency testing of cell-based immunotherapy medicinal products for the treatment of cancer
United States[5]
Process validation: General principles and practices
ICH[18]
Consideration all relevant biologics ICH guidelines
General principles to address the risk of inadvertent germline integration of gene therapy vectors (CHMP/ICH/469991/2006)
General principles to address virus and vector shedding (EMEA/CHMP/ICH/449035/2009)
ICH Topic Q5E Comparability of biotechnological/biological products
Pharmacopeia
PhEur monograph 5.14 Gene transfer medicinal products for human use (01/2010:51400)[19]
PhEur General Chapter 5.2.12. Raw materials of biological origin for the production of cell-based and gene therapy medicinal products[19]
2.7.23 Numeration of CD34+/CD45+ cells in haematopoietic products
USP General Chapters: <1046> Cell and Gene Therapy[20]

ICH, International Council for Harmonisation; PhEur, European Pharmacopoeia; USP, US Pharmacopeia.
[a]This list is not all inclusive.

European Union

At the time of writing, forthcoming adoption on quality, nonclinical, and clinical aspects of medicinal products containing genetically modified cells was expected in October 2020.[21] The update will include further guidance on:

- Reflection of experience gained with products at MAA, scientific advice and PRIME,
- Consideration of new tools for the genetic modification of cells (i.e., genome editing technologies),
- Reflection of the increase in clinical experience, especially with CAR-T cells and related products,
- Coverage of new categories of products (e.g., induced pluripotent stem cells), and
- Product comparability.

United States

The FDA's CBER notes in its guidance agenda for 2020, which delineates the guidance documents the center plans to release in 2020, that guidance specific to CAR-T cell therapies and products involving genome editing will be released by the end of 2020.[22] A guidance document addressing gene therapies for neurodegenerative disease also is planned. These will be draft guidances so there is currently no indication on the content. However, after draft guidances have been announced in the Federal Register, they will be open for public comment.

Take-home messages

The navigation of advanced therapy guidelines is not always intuitive to developers in the very early stage of development. This article provides a general pathway that developers could follow across the development phases of cell and gene therapy products. Advanced therapies are a fast-moving area and it is important to assess the latest guidance to capture any new advances.

Advanced therapy guidelines should be seen as enabling and helping with the overall development design and planning across nonclinical, CMC, and clinical development stages. They also provide an overview of what is required to meet regulatory expectations and requirements.

If you are developing advanced therapies, the best advice is to "live and breathe the guidelines." Guidance documents have been established and refined by combining expert input and insight from regulatory authority staff and industry stakeholders who are walking, or have walked, in the same development shoes.

Abbreviations

CAT, Committee of Advanced Therapies; **CBER,** Center for Biologics Evaluation and Research; **CGT,** cell and gene therapy; **CHMP,** Committee for Medicinal Products for Human Use; **EMA,** European Medicines Agency; **EU,** European Union; **FDA,** [US] Food and Drug Administration; **GMP,** good manufacturing practice; **ICH,** International Council for Harmonisation; **PhEur,** European Pharmacopoeia; **PRIME,** PRIority Medicine; **RMAT,** regenerative medicine advanced therapy; **US,** United States.

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