ThermoFisher SCIENTIFIC

Cell and gene therapies in the US vs. the EU

TOP FIVE AREAS OF DIFFERENTIATION

patheon

- API
- BIOLOGICS
- VIRAL VECTOR SERVICES
- EARLY & LATE PHASE DEVELOPMENT
- CLINICAL TRIAL SOLUTIONS
- LOGISTICS SERVICES
- COMMERCIAL MANUFACTURING

For cell and gene therapies (CGTs) and other complex biologics, US and EU regulatory processes vary by more than just jurisdictional oversight. In this eBook we share the five key differences in the drug development and review process for companies hoping to gain market access through US Food and Drug Administration (FDA) or European Medicines Agency (EMA) approval—as well as tips for navigating these differences.

Introduction

Despite long-term similarities in established drug categories such as small molecules, the US FDA and the EU EMA have not yet converged on guidance for emerging therapies such as CGTs and their counterpart category in the EU, Advanced Therapy Medicinal Products (ATMPs). With differences apparent even in product categorization, sponsors should familiarize themselves with regional variation as early in the development process as possible. Seeking regulatory guidance by taking advantage of each jurisdiction's additional communication opportunities for CGTs/ATMPs can help remove much of the uncertainty regarding development of these novel therapies in each region—particularly as development timelines can be condensed in this regulatory space.

Armed with the knowledge of key differences between the US and EU regulations, developers can proceed with confidence in their vendor selection and process decision-making. Awareness of the distinct classifications and manufacturing guidance by each region can also significantly aid in appropriate documentation of details required for successful market application in each jurisdiction.

1. Terminology: CGT vs. ATMP

The first key difference in US vs. EU regulatory processes is one of terminology. In the United States, CGTs are classified as biologics. CGTs include human gene therapy and cell therapy products, and human cells, tissues, and cellular- and tissue-based products (HCT/Ps). HCT/Ps fall under separate regulations. In the EU, all such products fall into the category of ATMPs. These are further subdivided into gene therapy, cell therapy, and tissue-engineered categories.

In addition to nomenclature, the different definitions of CGTs and ATMPs affect how a product may be classified in one jurisdiction versus another (see Table 1). While there is considerable overlap, the definitions are not identical, as they are based on regional regulations; sponsors must determine into which category their products fall to follow the proper steps toward review and approval.

Table 1. Definitions of CGTs vs. ATMPs for regulatory classification

Cell and Gene Therapies (US)[1]	**Human gene therapy** seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use.
	Cell therapy includes cellular immunotherapies, cancer vaccines, and other types of both autologous and allogeneic cells for certain therapeutic indications, including hematopoietic stem cells and adult and embryonic stem cells.
	Human cells, tissues, and cellular- and tissue-based products (HCT/Ps) are designed for therapeutic transplantation, infusion, and implantation procedures.[3]
Advanced Therapy Medicinal Products (EU)[2]	**Gene therapy** contains genes leading to a therapeutic, prophylactic, or diagnostic effect. It works by inserting "recombinant" genes into the body to treat a variety of diseases, including cancer, genetic disorders, and long-term diseases.
	Cell therapy contains cells or tissues manipulated to change their biological characteristics for the purpose of curing, diagnosing, or preventing disease.
	Tissue-engineered products contain modified cells or tissues to be used to regenerate, repair, or replace human tissue.

2. Guidance documents and governing regulations

Knowing which key laws and definitions govern the development, handling, and production of specialty biologics is the first step in achieving compliance and planning processes to facilitate success. Utilization of guidance documents and statements released by each agency can make the process more straightforward (Table 2).

Table 2. Jurisdiction-specific regulations and recent guidance documents

US laws governing biologics and CGTs

Food, Drug and Cosmetic Act (1938)

- Section 505 (Section 355 in US Code)

Public Health Service Act (1944)

- Section 351 (biologics and CGTs)
- Section 361 (human cells, tissues, and HCT/Ps per criteria in CFR 1271.10(a))

US CMC/quality guidance documents

- Manufacturing Considerations for Licensed and Investigational Cellular and Gene Therapy Products During COVID-19 Public Health Emergency (Guidance for Industry 2021)
- Chemistry, Manufacturing and Control (CMC) Information for Human and Gene Therapy Investigational New Drug Applications (INDs) (Guidance for Industry 2020)

EU regulations governing ATMPs

- ATMP Regulation 1394/2007/EC Commission Directive 2009/120/EC

EU CMC/quality guidance documents

- EudraLex Vol. 4, Part IV: GMP Requirements for Advanced Therapy Medicinal Products (2018)
- Q&A on the Principles of GMP for the manufacturing of starting materials of biological origin used to transfer genetic material for the manufacturing of ATMPs (EMA/246400/2021)
- Guideline on the Quality, Non-clinical and Clinical Aspects of Gene Therapy Medicinal Products (EMA/CAT/80183/2014)
- Guideline on Human Cell-Based Medicinal Products (EMEA/CHMP/410869/2006)
- ATMP Quality Flowchart and Checklist (2021)

3. Regulatory interaction and approval pathways

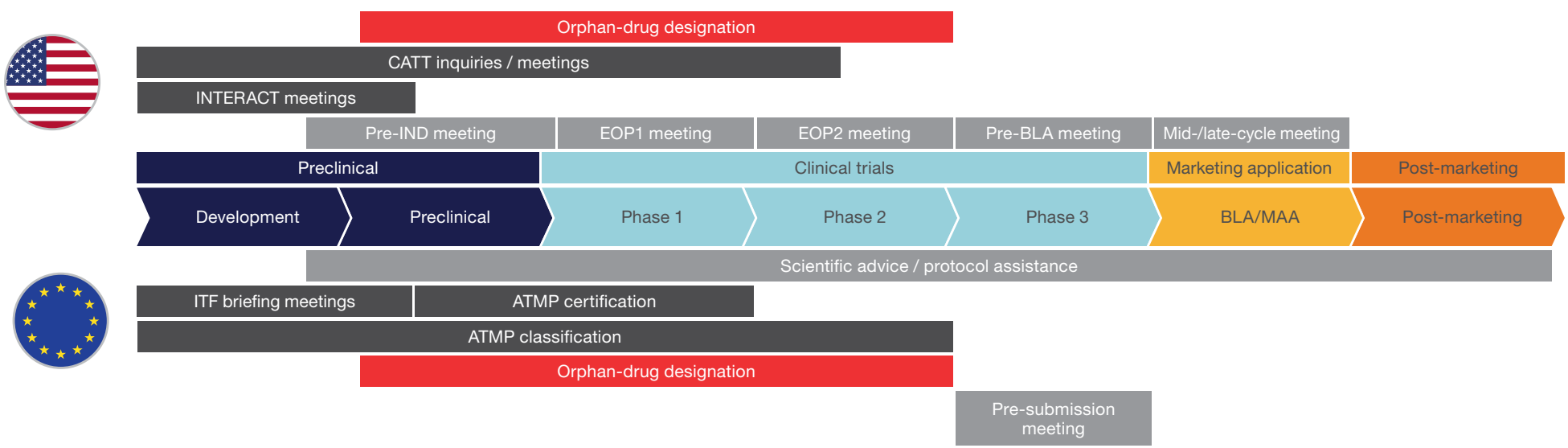
Due to the special nature and uncertainty inherent in bringing novel CGTs to market among both developers and regulatory agencies, additional opportunities are available for interaction with regulators throughout the development process in both the US and EU (Table 3). Eligibility for these meeting types varies by the type of product, however. There are also additional opportunities to qualify for specialty designations and review programs that can further increase regulator accessibility and the possibility of faster review timelines. Such programs include priority review, accelerated approval, fast-track status, breakthrough therapy designation, and regenerative medicine advanced therapy classifications in the US. In the EU, criteria are stricter for designation as an orphan drug, and accelerated assessment, conditional approval, and the Priority Medicines program (PRIME) exist as specialty program options depending on drug criteria.

In general, these meeting opportunities enable earlier and more frequent communication with regulators than is possible for other developers. They are weighted more heavily toward early interactions, but sponsors can meet with regulators throughout the entire process (Figure 1).

Table 3. Interaction opportunities for CGT/ATMP developers

US	• Initial Targeted Engagement for Regulatory Advice on CBER Products (INTERACT) • CBER Advanced Technology Team (CATT) • Type A, B, C, and D Formal Meeting Pathways
EU	• Innovation Task Force briefing meeting • ATMP Classification • ATMP Certification • Parallel Scientific Advice Meetings (EMA and/or National Competent Authority and/or Health Technology Assessment body)

Figure 1. Regulatory advice opportunities by phase of development. Dark gray indicates meetings only available for CGT/ATMP developers.



4. Manufacturing expectations

Because of eligibility for expedited review, CMC development timelines are often compressed for CGTs/ATMPs. Nonetheless, many similarities in US and EU manufacturing requirements exist. However, key differences in product classification can significantly alter inspection processes and documentation expectations. For example, viral vectors count as a biologic drug substance in the US, which typically dictates facilities be licensed and inspected for quality metrics related to vector purity, potency, safety, and handling. In the EU, however, viral vectors can sometimes be classified as starting materials, if used in a cell therapy or as an *ex vivo* gene therapy based on genetically modified cells; they may not always be subject to the same level of oversight as drug substances, but good manufacturing practices are often still required. This example makes it clear why it is essential to understand—very early in the process—how an investigational product is classified in each jurisdiction.

Regardless of these technicalities, the overall aim of each region's regulations is to protect patient health and safety. By understanding what elements of the drug product are critical components, and by demonstrating their purity, origin, and quality, developers should have sufficient data available to appease either agency. An experienced contract development and manufacturing organization (CDMO) can ease the management of differing expectations by product type.

Experienced CDMOs typically offer routine access to regulatory consultants and a range of regulatory support services, such as:

- CMC dossier writing
- Gap analysis and CMC dossier review
- CMC regulatory strategic consulting
- Health authority meeting, filing, and inspection support
- Familiarity with shifting regulatory guidelines

5. Commercialization requirements

Shorter timelines for approval based on filing pathways or special categorizations, as for orphan drugs, can create another challenge for CGT/ATMP development. In some cases, submission readiness comes more quickly than anticipated, and developers must make rapid decisions about scale-up, assays, and validation considerations. In other cases, the necessary small batch sizes required by starter material availability make ongoing production tenuous; changes in supply sources or quality require repeated validation that can quickly become costly and problematic. Planning a global submission strategy and selecting a competent manufacturing site, appropriate validation assays, and overall validation strategy early in development can smooth the transition to commercialization and support companies through jurisdictional variation in requirements for quality testing and manufacturing for distribution.

By understanding regional guidance and legislation related to commercial products before market approval, developers can plan for commercialization requirements sooner. This allows early preparation and selection of appropriate substances and vendors. Variability in assays and drug product potency is monitored by both the EMA and FDA, making the development of multiple assays or a matrix of product attributes advisable for ongoing quality demonstration. Coupled with proactive, effective scaling plans, thoughtful selection of manufacturing processes, and an experienced site, the growing pains associated with commercialization (even with differing requirements by country) can be greatly eased. Fewer than 90 CDMOs manage viral vector–associated products worldwide,[4] so selecting a site with experience and verified, appropriate licensing can make or break commercialization success.

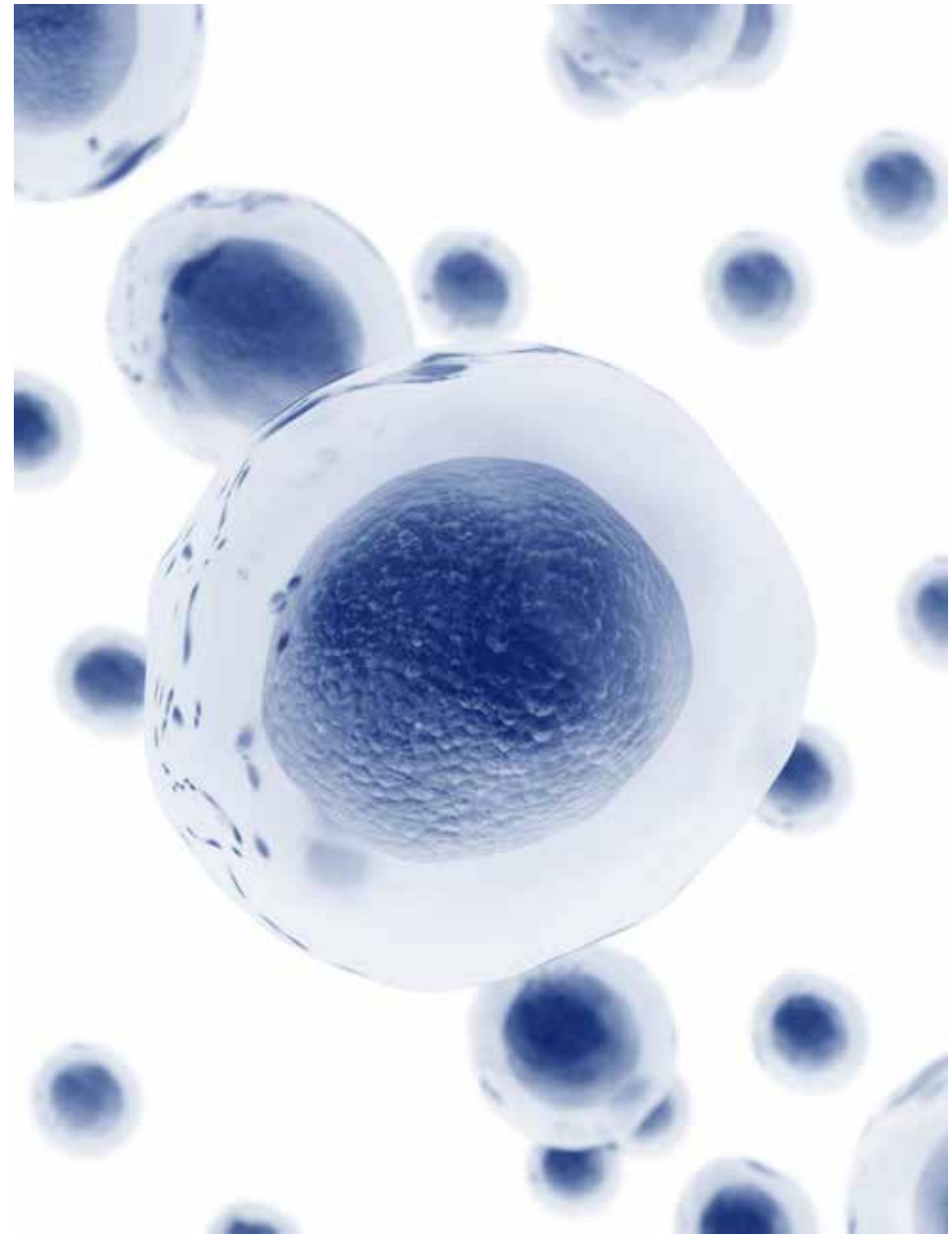
Additional considerations for commercial production site selection can be found in Figure 2.

Figure 2. Site selection considerations for reducing regulatory risk and improving product viability

Choosing the right site will help you to reach your regulatory milestones faster, reduce regulatory risk, and build for commercial success

Conclusion

As data accumulate from a growing number of CGT/ATMP approvals, regulators will obtain a better understanding of how safety, purity, and potency affect patients either in the clinic or in the market. Over time, regulators may converge on harmonized expectations as well. While sponsors await more formal guidance from each jurisdiction, they can utilize numerous tools to minimize the confusion and delay that can be caused by the differences in terminology and regulations between the FDA and EMA. From early consultation with research and CDMO partners to proactive selection of multiple assays and qualified production sites, sponsors can lay the groundwork for effective processes and approaches to minimize regulatory challenges and maximize their chances at market approval in both jurisdictions.



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Thermo Fisher Scientific provides industry-leading pharma services solutions for drug development, clinical trial logistics and commercial manufacturing to customers through our Patheon brand. With more than 65 locations around the world, we provide integrated, end-to-end capabilities across all phases of development, including API, biologics, viral vectors, cGMP plasmids, formulation, clinical trials solutions, logistics services and commercial manufacturing and packaging. Built on a reputation for scientific and technical excellence, we provide pharma and biotech companies of all sizes instant access to a global network of facilities and experts across the Americas, Europe, Asia and Australia. We offer integrated drug development and clinical services tailored to fit your drug development journey through our Quick to Care™ program. Our Quick to Clinic™ programs for large and small molecules help you balance speed and risk during early development so you can file your IND quickly and successfully. Digital innovations such as our mysupply Platform and Pharma 4.0 enablement offer real-time data and a streamlined experience. Together with our customers, we're rapidly turning pharmaceutical possibilities into realities.

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