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Building a proactive strategy for navigating regulatory complexity in CGT development and commercialization

The rapid advancement of cell and gene therapies (CGT) has created a dynamic regulatory environment that is complex and can be difficult to navigate. The lack of precedent and established frameworks for novel and evolving formats makes regulatory compliance especially difficult for biopharmaceutical manufacturers.

To bridge this disconnect and meet evolving regulatory mandates in the US, you should consider the following:

- **Creating a clear, effective strategy** that addresses regulators' concerns
- **Understanding and utilizing agency programs** and various special designations
- **Standardizing complex, variable manufacturing processes** to meet quality and compliance requirements

The following strategies can help you better understand how to fulfill your regulatory obligations and help avoid delays in commercialization.

CGT and Cencora

At Cencora, we have a passionate and patient-focused commitment to helping biopharmaceutical companies deliver revolutionary therapies to patients. In fact, Cencora has provided support in one or more ways for **over 80 percent of commercially available CGTs in the US and EU.**[1] From patient support programs, clinical study support, and global market access consulting, to logistics and distribution services, we provide industry leaders with the tools to help these therapies achieve their full potential. Cencora's CGT team of experts has identified these critical market challenges with recommendations on how best to address them.

Creating a clear, effective regulatory strategy

US regulatory agencies have introduced a variety of initiatives designed to facilitate a faster drug development process. These initiatives sometimes have similar or overlapping schedules, benefits, or requirements. It can be unclear which pathways to pursue so you can obtain the most valuable advice from these agencies.

Recommendation

A clearly defined regulatory strategy helps you with engaging regulators so you can maximize both efficiency and value. Your strategy also shows the regulatory agency your understanding of requirements and commitment to meet them, building trust and confidence.

Develop a Target Product Profile (TPP) to inform your regulatory engagement strategy. The TPP guides the development of therapeutic candidates, driving activities toward desired outcomes as well as identifying how you'll proactively mitigate potential regulatory risks.

Target Product Profile (TPP)

A well-executed TPP for your drug candidate outlines the following:

- Characteristics
- Benefits
- Target population and its identified unmet needs
- Treated disease definition and stage
- Differentiation from existing treatment options
- Potential side effects and associated risks
- Administration and dosage considerations
- Contingency planning

Early engagement in agency meetings will help you understand the regulatory agency and build key relationships. Each meeting has specific prerequisites and timelines. Knowing which meetings are required and how to frame your position can increase your odds of success. Examples of agency meetings include:

Initial Targeted Engagement for Regulatory Advice on CBER/CDER Products (INTERACT): This is an informal, exploratory meeting with the FDA that allows sponsors to receive early input on their development plans, as well as ask questions.

Pre-IND (Investigational New Drug): This meeting with the FDA takes place before you submit the IND and is more structured and focused on your clinical study strategy.

Prepare for all agency meetings with an agenda and have specific questions for regulators. An experienced consultant can help you draft a briefing document, frame the agenda, advise on critical question phrasing, and strengthen your clinical and epidemiological narrative.

Understanding the requirements of special programs and designations

Several special programs are available to help address CGT development burdens. The purpose of these programs ranges from expediting conditional approvals to accelerating development timelines. Each has different criteria and designations, making the requirements difficult for manufacturers to navigate and take advantage of their benefits.

Recommendation

Create a plan that can help you take advantage of these special programs and pursue those that fit your therapy model and program goals (See table). Collaborating with an experienced consulting team will help position you for success.

Examples of the FDA's special programs relevant to CGT

	Support for clinical Trials Advancing Rare disease Therapeutics (START) Pilot Program[2]	Regenerative Medicine Advanced Therapy (RMAT) Program[3]	Chemistry, Manufacturing, and Controls Development and Readiness Pilot (CDRP) Program[4]	Accelerated Approval (AA) Program[5]
Program purpose	To accelerate drug development for rare diseases by boosting communication with regulators	To accelerate development timelines, enhance guidance, and grant priority review to qualifying drugs	To improve the quality and efficiency of chemistry, manufacturing, and controls (CMC) development for new drug candidates, especially for rare disease and gene therapies	To enable expedited conditional approval of qualifying drugs
Key program features	• Enhances early communication between agency and developers • Aims to better inform development strategy and shorten time to submission	• Provides enhanced guidance and communication with FDA • Allows surrogate endpoints • Enables eligibility for AA	• Streamlines CMC review and agency response • Provides tailored CMC feedback to ensure compliance and feasibility	• Allows surrogate and intermediate endpoints • Requires sponsor to complete confirmatory and post-market studies • Maintains the burden of proof on the sponsor
Eligibility criteria	• Address a serious or life-threatening condition • Employ an innovative or novel approach • Show strong pre-clinical evidence • Be willing to engage with FDA	• Address a serious or life-threatening condition • Be a regenerative medicine drug candidate • Demonstrate potential for significant improvement over standard of care	• Engage early in the development process • Provide strong CMC data • Have an active commercial IND in Electronic Common Technical Document (eCTD) format • Show commitment to pursue CMC development plan that aligns with expedited development	• Address a serious condition • Have surrogate or confirmatory endpoints, and justification • Complete confirmatory studies and meet study endpoints
When to request	Early in development, when in clinical trials under an active IND	Once the potential for significant improvement over existing therapies can be demonstrated, with an IND submission as an amendment to an existing IND	Before end of Phase 2, when under an active IND with an expedited clinical development timeframe	Once the pivotal study has begun and after meeting with agency to discuss requirements and appropriateness

Standardizing manufacturing processes to meet CMC requirements

CMC requirements are designed to ensure safety, efficacy, and consistency in the drug development and production process. However, it's challenging to standardize manufacturing processes for complex biologicals that contain variable materials, have inherent variability between batches, and may be difficult to scale up. You must address two major hurdles that are crucial for meeting regulatory requirements:

Potency, which ensures the product elicits the desired therapeutic effect at the intended dose, is challenging to accurately measure and maintain.[6] This is due to the products' biological variability or nuances in manufacturing.

Comparability, which ensures that different batches maintain consistent quality, efficacy, and safety profiles, is difficult to demonstrate for some CGTs.[7] Changes made over the course of clinical development or in manufacturing processes can significantly impact product characteristics and performance.

Recommendation

Save time and money by monitoring process changes during development. Consulting experts in process development and technology transfer can help you establish effective methods for comparative analysis across the development journey.

Reduce the risk of delays and align product quality testing with regulatory expectations by identifying critical quality attributes (CQAs) for your product's safety, efficacy, and quality. For instance, a **potency** CQA, which relates to your drug's mechanism of action and clinical efficacy, helps ensure the final product is consistently manufactured "as it may relate to the safety or effectiveness of the product."[8] A potency CQA should be measurable, scalable, and reasonable to assess during the compressed timelines of a commercial program.

For effective batch **comparability** tests, retain samples from Phase 1 trials so you can establish parameters for later phases and establish a comparability narrative throughout development. The ideal potency assay should be quantitative, indicate stability, and confirm lot-to-lot consistency. Since manufacturing processes and potency assays may change during development, monitoring and controlling them is crucial to ensure the final product meets regulatory standards for drug substance safety and quality.[7]

What is chemistry, manufacturing, and controls (CMC)?

CMC is a critical aspect of drug development that details the composition, manufacturing processes, quality control, and stability of a drug product. It ensures that the drug is consistently produced and controlled to meet quality standards.

For more insights and support to help with commercializing your CGT, visit Cencora.com

References

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