FDA Oversight of Cell Therapy Clinical Trials

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The U. S. Food and Drug Administration applies regulatory flexibility to balance benefits and risks to subjects in cell-therapy clinical trials.

Investigational cell therapy products—including those derived from stem and progenitor cells—hold great promise for addressing unmet medical needs but also present challenges related to product characterization, safety testing, and clinical trial design (Fig. 1). The U.S. Food and Drug Administration (FDA) adapts to the changing landscape of this evolving field by applying flexible regulatory standards that balance benefits and risks to those who take part in clinical trials. In this Focus, we describe the FDA’s process for facilitating the development of safe and effective cell therapy products and highlight the importance of information sharing and transparency in the regulatory decision-making process.

DEVELOPING SAFE CELL THERAPY PRODUCTS

FDA’s primary objectives in the oversight of clinical trials involving cell therapy products are to (i) assure the safety and rights of trial participants and (ii) ensure that the quality of the scientific evidence is adequate to permit an evaluation of the product’s effectiveness and safety. In regulating cell therapy products, FDA takes into account the scientific and medical information currently available and complements internal expertise by engaging outside scientific and clinical experts, the patient community, and other stakeholders through various mechanisms, including scientific workshops and advisory committees. To ensure that the public has an opportunity to participate at these meetings, time is allotted for public comments.

When FDA proposes a new regulation, input from stakeholders and the public is solicited through a formal notice and comment process that provides a pathway through which all interested parties can supply written input to FDA (1). By following such an approach, FDA’s Center for Biologics Evaluation and Research (CBER) hopes to facilitate free exchange of ideas and information among all interested parties, which is of particular importance when developing regulatory policy in a new field of research. To promote maximum transparency of the regulatory decision-making process, all relevant regulations and guidance documents are available online or through other publicly accessible means (2). FDA staff members also conduct intramural research to investigate the fate and function of transplanted cells and to improve cell product testing strategies. Outcomes from intramural research assist FDA’s decision-making process in the evaluation of cell therapy products. FDA staff members are also involved in clinical trial design research to improve strategies for clinical evaluation of the safety and efficacy of cell therapy products.

In the United States, clinical trials of all cell therapy products that require licensure, but have not yet been approved, must be performed under an Investigational New Drug (IND) application (3) with oversight from CBER (for example, see Fig. 1). INDs are reviewed by FDA scientists with expertise in product chemistry, manufacturing, and controls (CMC) as well as preclinical testing and clinical trial design for cell therapeutics. Prospective IND applicants are encouraged to communicate early with FDA regarding their product development program through informal interactions and formal pre-IND meetings. During this early engagement, prospective IND applicants and FDA scientists discuss both general and specific issues regarding overall product development strategy and ways to ensure that sufficient information is generated to justify the initiation of a clinical trial.

CMC CONSIDERATIONS

Throughout clinical development, the most important CMC review issue for cell therapy products is the administration of a safe product to the subject. Thus, meticulous attention must be paid both to the source of the cells and to preventing the introduction of microorganisms during the manufacturing process.

Microbiological safety is most effectively implemented through source control, which includes qualification of the cell or tissue donor and control of all materials used in manufacture. As a minimum requirement, donors of living cells must be screened and tested for relevant communicable disease agents and diseases (4). All materials used in product manufacturing must be qualified by certification from the vendor, tested by the end user, or both in order to ensure that they are free of adventitious agents (microorganisms introduced unintentionally) and are otherwise of suitable quality for their intended use. Because of potential exposure to animal viruses, product components derived from animal material present additional qualification concerns. Further, in the United States, human cells or tissues intended for human administration that come into direct contact with live nonhuman animal cells during product manufacture are considered xenotransplantation products, warranting additional microbiological testing (5).

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It is crucial to identify product attributes that will reliably predict safety and effectiveness. This can be a formidable challenge, especially for stem cell–derived products, which may undergo further differentiation at the time of administration into human subjects or subsequently. To arrive at a predictive set of tests, one must explore a wide variety of product characteristics such as morphology, synthesis and release of bioactive factors, gene expression profiles, and other attributes indicative of cell identity or viability. These investigations should be initiated during the early stages of product development (that is, before and during phase 1 and 2 clinical trials). Once appropriate attributes and tests are conceived, product developers need to confirm the ability of the manufacturing process to yield a consistent final product with the desired characteristics. In 2008, FDA amended current good manufacturing practices (cGMP) regulations (6) to exempt most investigational phase 1 drugs from complying fully with the cGMP regulations. In an accompanying guidance (6), FDA provides recommendations on approaches to comply with the basic concept of cGMP for this early-phase material. As product development proceeds, the manufacturing process should be refined, culminating with full cGMP compliance at the time of licensure.

As with other biological products subject to FDA’s biologics regulations, licensed cell therapy products need to be tested for safety, identity, purity, and potency (7). In contrast, during the investigational phase, which includes all phases of clinical trials before marketing authorization, FDA requires sufficient information “to assure the proper identification, quality, purity, and strength of the investigational drug” (7). CBER has flexibility in determining which tests are appropriate to meet the regulatory requirements for these products. The regulations also require that an identity test be designed to ensure that the investigational product is identical to what is described on its label and can be distinguished from other products manufactured in the same laboratory (7). CBER expects implementation of an identity test for early clinical trials to ensure that the participant receives the intended product. All phases of clinical investigation require purity testing, which encompasses sterility and the absence of endotoxins or other undesired components. Other aspects of establishing a purity/impurities profile present challenges in early phases of development when product characterization data are often limited. Although the final product may not be a homogeneous population of identical cells, it is important to minimize the percentage of cells with undesired characteristics (for example, undifferentiated or misdifferentiated cells) in the final product. At a minimum, the various cell populations should be characterized to the extent feasible and should be as consistent as possible between preparations.

As for all licensed biologics, a measurement of potency is required. Potency is defined by FDA biologics regulations as “the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result” (8). Development of meaningful and relevant potency assays for cell therapy products necessitates extensive product characterization. Measures of potency may be demonstrated using in vitro and/or in vivo tests, as appropriate. This topic is discussed in detail in FDA’s guidance on potency tests for cell and gene therapy products (8).

**PHARMACOLOGY AND TOXICOLOGY**

Preclinical pharmacology and toxicology studies are conducted to characterize the safety profile of a cell therapy product before its administration to clinical trial participants. The complex nature of these investigational products precludes the application of a traditional toxicology program; the design of the preclinical studies is therefore formulated on a case-by-case approach. The selection of animal species, animal models, product delivery systems, study duration, and study endpoints (biochemical, functional, and morphological) will depend on the known biological attributes of the product, the anticipated mechanism of action of the product, the target disease population, and the proposed clinical trial design.

The invasive routes of administration and presumed permanence in vivo, as well as the potential for (i) inflammatory reactions in target and nontarget tissues, (ii) host immune response to the product, (iii) differentiation to undesired cell and tissue types, and (iv) unregulated or dysregulated cell proliferation (that is, tumor formation), raise safety concerns about cell therapy products. Therefore, the conduct of preclinical studies to provide support for a reasonable expectation of clinical benefit is important. Well designed proof-of-concept (POC) studies in appropriate animal models of disease or injury can provide a level of confidence that the scientific rationale for initial human studies is sufficiently sound to justify the risks of product administration. In addition, POC studies help to determine a pharmacologically effective dose range and dosing regimen, optimize the route and timing of product administration relative to disease progression, and elucidate the in vivo outcome of the administered cells (9).

Addressing these questions will help to inform clinical trial design.

In order to complement POC studies in defining the risk-benefit profile of a cell therapy product, toxicology studies are conducted to identify, characterize, and quantify potential local and systemic adverse effects resulting from the cell therapy product itself and the product administration procedure. In many instances, assessment of the toxicology parameters can also be addressed in the POC studies. Data generated from toxicology studies should help define a potentially safe dose range, as well as identify safety signals that may be useful in developing an appropriate clinical monitoring plan.

The preclinical testing paradigm for each cell therapy product can differ in complexity, scope, and design; thus, early communication with CBER staff is strongly encouraged. These interactions help to accelerate the translation of research and to ensure consideration of the 3Rs—refinement, reduction, and replacement—of animal use (10).

**CLINICAL TRIAL DESIGN**

FDA oversight of the safety of cell therapy products in clinical trials includes consideration of the nature of the product and the proposed anatomical site and method of product administration. Early-phase trials of cell therapy products differ markedly from typical phase 1 small-molecule drug trials because of the substantial differences between the two product types. In contrast to most drugs, cell therapy products are administered without terminal sterilization; furthermore, after administration the anatomical distribution, duration of action, and product life span are often uncertain. For example, unchecked cell proliferation, as opposed to exponential decay of drug concentrations, is a possibility for some cell therapy products. In addition, dose determinations are far less precise for cell therapy products than for small-molecule drugs. The possibility of immune rejection or other
unanticipated immunological responses must also be addressed. The anatomical sites of administration (for example, intracranial, intraspinal, or intracardiac) proposed for many cell therapy products may pose additional safety risks arising from the surgical procedures, the vulnerabilities of the sites themselves, and subsequent accessibility of the sites in the event of medical necessity, including the need for product removal. Given these considerations, it is important that sponsors provide sufficient preclinical safety data and rationale to support the initial starting dose and dose escalation scheme proposed in the clinical study protocol. Finally, the risks of investigational cell therapy products, including administration procedures and concomitant medications, are generally too great to permit the study in healthy volunteers. Therefore, unlike many phase 1 drug trials, participants in trials for a cell therapy product have the targeted disease, which is often serious or life-threatening. Such individuals may require ongoing treatments and medications, which have the potential to interact with the cellular product.

Safety monitoring procedures employed during clinical trials of cell therapy products should be based on potential product-specific adverse outcomes that may emerge over a protracted period. Cell therapy products may consist of heterogeneous cell populations and may exhibit a variety of properties that reflect the specific cell mixture, including the capacity for proliferation, further differentiation, migration, and functional physiological or pathological integration into target tissues. Monitoring methods in early-phase trials should be chosen after considering the full capabilities of existing technologies and analytical tools applied over appropriate periods, in order to provide adequate safety assessment and to measure potential therapeutic benefits or pharmacodynamic actions of the cell product. The duration of long-term follow-up will depend on the nature of the product and the specific disease indication. There is a great need for the development of biomarkers of safety and efficacy to characterize the effects of such products in trial participants. Furthermore, improvement in cell tracking techniques, especially those based on noninvasive imaging modalities that can be used clinically, would aid in safety monitoring and could help facilitate the understanding of the clinical effects of this product class.

Last, at all stages in the regulatory process, FDA encourages open and transparent communication among participants in the cell therapy field—academic and commercial researchers, patient interest groups, funding agencies, and regulators—to help facilitate the development of safe and effective cell-based therapies.

REFERENCES AND NOTES


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