SPECIAL REPORT

Balancing Safety and Innovation for Cell-Based Regenerative Medicine

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Regenerative medicine is a field that involves replacing, engineering, or regenerating human cells, tissues, or organs to establish, restore, or enhance normal function.[1] It is an area with great promise that goes directly to the role of the Food and Drug Administration (FDA) in helping to facilitate the availability of safe and effective treatments. The broad scope of regenerative medicine products includes cell therapies, therapeutic tissue-engineering products, human cell and tissue products, and certain combination products involving cells and devices, such as scaffolds upon which cells can grow. Recently, there has been much interest specifically in the potential of adult stem cells to address a wide variety of conditions.

THE EXPANDING USE OF STEM-CELL–BASED PRODUCTS

Advances in the field of hematopoietic stem-cell biology have led to the development of treatments such as hematopoietic stem-cell transplantation (HSCT), which has been associated with improved survival for patients with benign and malignant hematologic disorders.[2] However, despite the increasingly widespread use of stem cells in techniques being labeled as regenerative medicine, clinical benefit has not been clearly shown in most instances. What can be done to help advance the development of safe and effective cell-based products in the field of regenerative medicine?

Scientific advances have shown us that stem cells are indeed remarkably complex biologic entities. To complicate matters, the term "stem cells" has been used to describe a variety of cells that have the capacity to divide and differentiate, including hematopoietic stem cells and adipose-derived stem cells (mesenchymal stem cells). The potential benefits to human health have spurred major progress in stem-cell biology over the past several decades. The field has moved from characterization of the properties of these cells toward therapeutic applications. This history is instructive in informing our current policy.

Today, there are thousands of citations in the literature related to clinical HSCT that have clearly documented the side-effect profile and efficacy of such procedures. Yet such scientific and clinical progress in HSCT contrasts with the current situation for a number of other stem-cell products, such as mesenchymal stem cells. Despite a proliferation of early-phase trials of mesenchymal stem cells, definitive studies regarding the safety and efficacy of such procedures as compared with the standard of care have been lacking.[3,4] For example, mesenchymal stem cells have been used in patients with a wide range of conditions, from cancer to disorders affecting the central nervous system, including Alzheimer's disease, despite the paucity of information from well-designed clinical trials. Two explanations that are often cited as to why mesenchymal stem cells should be safe and effective for so many different conditions are that the cells are immunomodulatory and that they can differentiate appropriately on the basis of the environment into which they are introduced. We now know with reasonable certainty from the scientific literature that this is not always the case.

At the same time, the administration of such stem cells may be associated with serious adverse events.[5,6] Even in the absence of serious adverse events, the use of therapies that are of unproven efficacy is a disservice to patients and to public health. An increasing number of safe and effective therapies are becoming available on the basis of the findings of well-designed clinical trials. It is critical to focus on efforts to

facilitate the development of such therapies, rather than propagating products with dubious clinical efficacy and possible risks. Facilitating the availability of safe and effective therapies is the aim of the FDA's recently released comprehensive policy framework for the development and oversight of regenerative medicine products, including new stem-cell therapies.

REGULATORY CONTEXT FOR REGENERATIVE MEDICINE

HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS

To put this comprehensive policy framework in perspective, the FDA's statutory authority in this area is based in part on the Public Health Service Act. Section 351 of this act provides the FDA with authorities surrounding the licensure of biologic products, and Section 361 mandates that the agency will issue and enforce regulations necessary to prevent the introduction, transmission, or spread of infectious disease. That regulatory framework is risk-based and divides human cells, tissues, and cellular and tissue-based products (HCT/Ps) into those requiring and those not requiring premarket approval. The products that are regulated under both Sections 351 and 361 of the act are biologic products and must be studied under the provisions for investigational new drugs. In addition, the manufacturers of such products are required to submit a biologics license application to the FDA for approval before marketing. In contrast, the products that are regulated solely under Section 361 and under the implementing regulations do not need premarket approval. Instead, they require registration and listing with the FDA before marketing, provided they are produced in compliance with the appropriate provisions to prevent the transmission of infectious diseases.

The decision regarding which regulatory pathway a given product must follow rests in part on whether the product meets or does not meet the criteria of the regulations promulgated under the Code of Federal Regulations part 1271 of Title 21, which have been in place since 2005. In brief, products that are regulated solely under Section 361 generally are those that do not undergo substantial processing (minimal manipulation), are used in a manner in the recipient that is similar to that in the donor (homologous use), are not combined with another drug or biologic product, and do not have a systemic effect, unless they are designed for autologous transplantation, first- or second-degree–related allogeneic transplantation, or reproductive use (Table 1). Examples include corneas and heart valves. Such cells and tissues are subject to FDA regulations only to prevent the transmission of communicable diseases. All other HCT/P products are regulated as drugs, biologics, or devices and require appropriate regulatory submissions for the conduct of clinical trials and marketing.

Table 1. Categories of Human Cells, Tissues, or Cellular and Tissue-Based Products (HCT/Ps).

HCT/P
Cardiovascular tissue
Cell-derived therapeutic products (e.g., pancreatic islets, mesenchymal stem or stromal cells, fibroblasts)
Dura mater
Hematopoietic progenitor cells derived from peripheral or cord blood (including hematopoietic stem cells)
Musculoskeletal tissue (include adipose-derived stem cells)
Ocular tissue
Placenta or amnion
Reproductive cells and tissues
Skin
Not HCT/P
Blood vessels that are a part of an organ intended for transplantation
Human collagen
Human milk
In vitro diagnostic products
Minimally manipulated bone marrow for homologous use and not combined with another article (with a few exceptions described in the tissue regulations)
Nonhuman cells, tissues, or organs
Vascular composite allografts
Vascularized human organs for transplantation
Whole blood or blood components, including platelet-rich plasma

EXPEDITING THE DEVELOPMENT OF NEW THERAPIES

The FDA recognizes the time and effort that go into the creation of regulatory submissions and the effect that working through the regulatory process can have on the time lines for the development of innovative products. Although the

FDA has traditionally focused on ensuring the quality, safety, and efficacy of medical products, its mandate has expanded to encompass a role in expediting the development of new therapies, particularly those aimed at serious or life-threatening conditions. The expedited programs — including fast-track designation, priority review, accelerated approval, and designation as a breakthrough therapy — have been successful in accomplishing this goal.[7] The role of the FDA in facilitating innovation while upholding the agency's approval standards, especially when it comes to areas of unmet medical need and new technologies, is also clearly expressed in the legislative initiatives contained in the 21st Century Cures Act, which was enacted on December 13, 2016.

To facilitate therapeutic advances from stem-cell therapies, along with other HCT/Ps, the 21st Century Cures Act introduced an additional expedited program in which a product is designated as a regenerative medicine advanced therapy (RMAT). This designation provides sponsors of a qualified regenerative medicine product that is intended for the treatment of serious or life-threatening conditions with advantages similar to those of the breakthrough-therapy designation, provided that preliminary clinical evidence indicates that the therapy addresses unmet medical needs. The simple requirement for preliminary clinical evidence of efficacy distinguishes RMAT from the breakthrough designation, which requires preliminary clinical evidence of a substantial improvement over existing therapies. In addition, RMAT-designated products that receive accelerated approval may be eligible to use an expanded range of options to fulfill their post-approval commitments. Such options include the use of traditional studies as well as the submission of patient registries or other sources of real-world evidence. As of December 29, 2017, the FDA had received 43 requests for RMAT designation, had acted on 35 of these requests, and had granted 13 of them.

COMPREHENSIVE FRAMEWORK FOR REGENERATIVE MEDICINE

In November 2017, building on these policy and scientific opportunities, the FDA released a comprehensive framework for the oversight of regenerative medicine to help the field continue to advance. This regulatory framework is articulated in two final and two draft guidance documents (Table 2). Since the FDA is highly cognizant of the importance to sponsors of the distinction between therapies that require premarket authorization and those that do not, the FDA's new policy framework more clearly describes for the developers of regenerative medicine therapies how these distinctions are made under the regulations, particularly with regard to the criteria for minimal manipulation and homologous use. The FDA strove to take a modern approach to existing regulations and statutes, balancing the objective of fostering expedient development of innovative products for patients who have medical needs with the need to ensure that such therapies are both safe and effective. As part of the regulatory framework, the FDA also articulated a risk-based compliance and enforcement policy. This policy will allow developers of lower risk products up to 36 months from November 16, 2017, to determine whether they need to submit an application for an investigational new drug or a marketing application in light of the recently published guidance documents and, if such an application is needed, to prepare the new-drug or marketing application. The FDA intends to take additional enforcement actions in cases in which it believes unproven products may put patients at risk.

Working within the existing regulatory framework, the FDA will make use of all available regulatory pathways and will adopt the use of some new principles that we believe will make the appropriate premarket evaluation of stem-cell–based therapies more efficient. On a large scale, the FDA will be incorporating some new concepts for how small investigators and firms can seek and meet the approval standard for products through efficient, expedited pathways.

For example, the FDA will provide tools to encourage individual or small groups of physicians to collaborate in support of the development of a stem-cell or other regenerative medicine product, which will ultimately lead to the receipt of a biologics license by each of the physicians or groups (Fig. 1). How might this work? The investigators who manufacture the product will need to agree on and follow a common manufacturing protocol and develop a com-

Table 2. Four Guidance Documents Describing the Regenerative Medicine Framework.*

Document	Summary	Example
Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception — Final	Addresses the criteria required for the exception, the types of procedures generally considered to be the same surgical procedure, and what processing steps can be undertaken to still meet the exception. In essence, this guidance clarifies how the regulations apply in order to facilitate the optimal care of patients undergoing surgical procedures.	A situation in which this guidance would apply is when a piece of the skull is removed for decompression after traumatic head injury. The bone may be minimally processed, stored, and then returned to the patient a few weeks later when the acute event is over, without the need for regulatory interaction with FDA.
Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use — Final	Provides FDA's interpretation of the existing regulatory definitions of minimal manipulation and homologous use. The guidance clarifies that these are distinct concepts and notes how to determine whether an HCT/P has been minimally manipulated or is intended for homologous use. The guidance also describes the compliance and enforcement policy that the FDA will use for HCT/Ps. For the first 36 months after issuance of the final guidance in November 2017, the FDA intends to exercise enforcement discretion for certain products that pose a low risk to public health so that sponsors will be able to have a dialogue with the agency and file the appropriate regulatory documentation.	Adipose tissue is considered to be a structural tissue for the purpose of the regulatory framework. This is relevant to determining the appropriate regulatory pathway for stem cells derived from adipose tissue, which in many applications will be regulated under both Sections 351 and 361 of the Public Health Service Act.
Evaluation of Devices Used with Regenerative Medicine Advanced Therapies — Draft	Provides a comprehensive resource to developers of devices used with RMATs. Topics covered include how the FDA will simplify and streamline its application of regulatory requirements for devices and cell–tissue combination products.	Under certain circumstances, a device that is used with an RMAT might be classified as a class III device or be limited to a specific intended use with only one type of cell.
Expedited Programs for Regenerative Medicine Therapies for Serious Conditions — Draft	Provides information about the expedited programs available to RMATs, including fast-track and breakthrough-therapy designations, and describes the FDA's considerations in implementing the new expedited program for RMATs. The guidance also describes an innovative program using cooperative development open to regenerative medicine products.	Multiple sites that manufacture a product using a common process may collaborate on clinical trials as part of a development program, which ultimately results in biologics licenses for each of the individual sites.

* The listed guidance documents can be accessed at www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm585218.htm. RMAT denotes regenerative medicine advanced therapy.

mon clinical trial protocol. Each site will then produce the product to treat the patients who are enrolled in the clinical trial at its own site. Subsequently, the pooled safety and efficacy data from the various sites that are participating in the trial will be submitted as part of a biologics license application for each.

If the clinical data that are submitted in conjunction with the manufacturing information show a favorable benefit–risk profile, the FDA could rely on that pooled data in determining whether the product is safe and effective. The agency would then issue a stand-alone biologics license to each of the physicians or groups so that each could proceed to produce the product independently. This approach, with appropriate planning and statistical analysis, would provide an alternative to how development generally has been conducted in the past to support approval. Such a pathway toward licensure may be well suited to groups of investigators or small firms that are able to consistently follow a common manufacturing and clinical protocol but that may not have access to the patient populations or infrastructure needed to conduct separate development programs. The approach may be particularly well suited to the development of products that involve manufacturing that is not highly complex yet is more than minimal manipulation and to clinical applications amenable to trials of relatively simple design.

Such an approach is just one example of how the FDA is taking an original policy approach to the regulation of a highly innovative field, one in which our traditional approach to regulation may not be as efficient or effective as in more

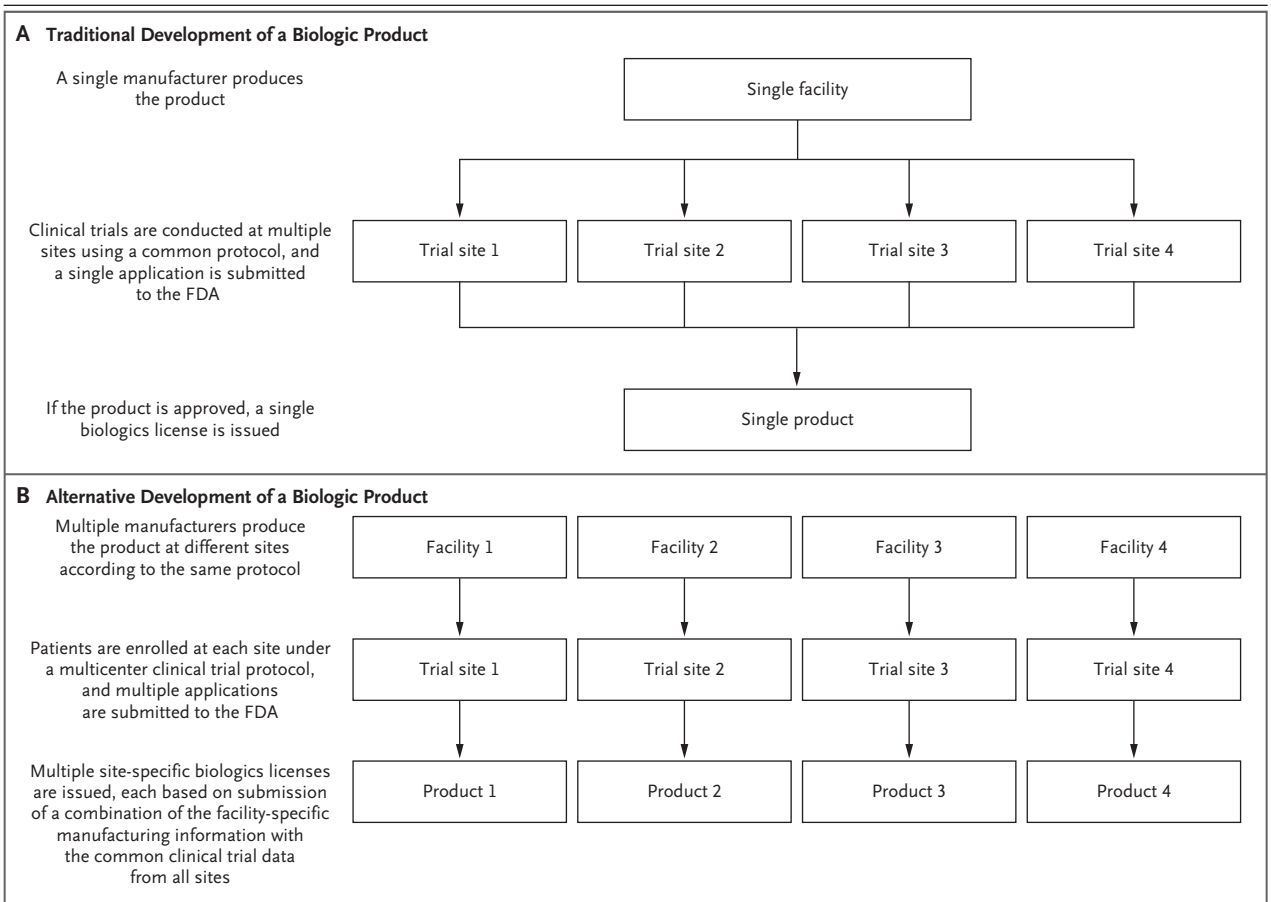

Figure 1. Traditional versus Alternative Development of a Biologic Product.

In the traditional development pipeline (Panel A), a single manufacturer produces the product at a single manufacturing facility and sponsors the clinical trials, which are conducted at multiple clinical sites. The manufacturer ensures that the product is manufactured consistently with appropriate quality control for use at each site and that it is administered pursuant to the protocol. The manufacturer then collects and analyzes the data from the clinical trials and submits a biologics licensing application to the Food and Drug Administration (FDA). If the product is approved, the manufacturer then receives a biologics license to produce and distribute the product. As an alternative to this process (Panel B), multiple manufacturers, which may be individual physicians or groups of physicians, enter into a cooperative development agreement. These manufacturers then produce the product at different sites according the same protocol, which includes appropriate quality-control procedures to help ensure consistency between different lots produced at different sites. Patients are enrolled at each of the sites that are manufacturing the product in a multicenter clinical trial protocol. Once the data from the multicenter trial are analyzed to evaluate the safety and efficacy of the product, the individual physicians or groups of physicians submit a biologics licensing application that includes the manufacturing protocol used, the clinical data obtained at the individual site, and the results of the multicenter clinical trial showing safety and efficacy. This ultimately results in the issuance of a site-specific biologics license for the product made by each physician or group of physicians.

mature fields. As part of its efforts in the area of regenerative medicine, the FDA is also encouraging investigators who are involved in innovative product development to engage in dialogue with the agency early on in the process, including through informational meetings, before more formal discussions are held about submitting an application for an investigational new drug. (Additional details about this process can be obtained by emailing industry.biologics@fda.hhs.gov.) Our aim is to refashion our traditional tools for regulation to meet the challenges and opportunities presented by such highly innovative products as cell-based regenerative medicine.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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