

HEALTH POLICY REPORT

FDA Regulation of Stem-Cell–Based Therapies

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In the interest of public safety, the Food and Drug Administration (FDA) has jurisdiction over the production and marketing of any stem-cell–based therapy involving the transplantation of human cells into patients. The FDA’s recently promulgated regulations regarding human cells, tissues, and cellular and tissue-based products¹ provide an appropriate regulatory structure for the wide range of stem-cell–based products that may be developed to replace or repair damaged tissue.

Basic and clinical scientists, as well as scientists working in the biotechnology and pharmaceutical industries, need an increased awareness of the questions that must be answered before a stem-cell–based product can be used clinically. Unlike pharmaceutical products, many stem-cell–based products may originate in academic laboratories where researchers are unfamiliar with the applicable regulations. We outline here the existing regulations regarding cell and tissue products that the FDA is likely to apply to the preclinical development and testing of various types of stem-cell–based therapies. We also make specific recommendations about how scientists should address the inherent safety and efficacy issues associated with these therapies.

 THE REGULATORY FRAMEWORK
FOR STEM-CELL–BASED PRODUCTS

Stem-cell–based therapies have existed since the first successful bone marrow transplantations in 1968.^{2,3} The recent development of techniques to grow human embryonic stem cells in culture⁴ and an increased understanding of the pathways of cell differentiation have expanded the horizon of likely therapeutic uses. This article focuses on a subgroup of these applications — the use of embryonic pluripotent or adult multipotent stem cells to create human tissues *ex vivo* for transplantation into patients with medical conditions caused by the degeneration or injury of cells, tissues, and organs. Such replacement tissues may or may not include stem cells in the final

product. In some cases, multipotent cells might be transplanted, which would give rise to terminally differentiated cells *in vivo*. In other cases, it might be desirable to allow the cells to differentiate fully in culture before transplanting them or to transplant a mixture of multipotent cells and differentiated cells. To encompass these variations, we use the term “stem-cell–based products.”

As a class of therapeutic agents, stem-cell–based products meet the definitions of several different kinds of regulated products: biologic products,⁵ drugs,⁶ devices,⁷ xenotransplantation products,⁸ and human cells, tissues, and cellular and tissue-based products.^{1,9} The last category — human cells, tissues, and cellular and tissue-based products — is defined as “articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.”¹⁰ By definition, any therapies that are considered to be stem-cell–based products fall into this category and thus are subject to the regulations that govern these products.

Any stem-cell–based product that contains cells or tissues that “are highly processed, are used for other than their normal function, are combined with non-tissue components, or are used for metabolic purposes”^{11,12} — and that includes most, if not all, of them — would also be subject to the Public Health Safety Act, Section 351, which regulates the licensing of biologic products and requires the submission of an investigational new drug application to the FDA before studies involving humans are initiated. (See Table 1 for highlights of the regulations regarding human cells, tissues, and cellular and tissue-based products and biologic products.)

 DEMONSTRATION OF PRECLINICAL
SAFETY AND EFFICACY

Before filing an investigational new drug application for a stem-cell–based product, the applicant

Table 1. Highlights of Regulations Applicable to Stem-Cell–Based Products.**Human cells, tissues, and cellular and tissue-based products**

The governing statute is Public Health Safety Act, Section 361.

The major objectives of this statute are to prevent the use of contaminated tissue, limit the improper handling of tissues, and ensure the clinical safety and efficacy of cells or tissues that “are highly processed, are used for other than their normal function, are combined with non-tissue components, or are used for metabolic purposes.”^{11,12}

Different standards apply, depending on the seriousness of a disease and an assessment of the potential risks and benefits of the treatment.¹³ These standards are consistent with the regulations governing accelerated approval of therapies for serious or life-threatening illnesses.¹⁴

This statute is supplemented by FDA guidance documents, which will need to be expanded or revised to address specific issues regarding stem-cell–based therapies and to clarify the definitions of “highly processed” and “used for other than their normal function.”^{11,15–18}

Biologic products

The governing statute is Public Health Safety Act, Section 351.

Any stem-cell–based product that includes cells or tissues that “are highly processed, used for other than their normal function, are combined with nontissue components, or are used for metabolic purposes”^{11,12} will be regulated as a biologic product.

As currently envisioned, most, if not all, stem-cell–based therapies will be considered to be biologic products.

The manufacturer of a biologic product must demonstrate that it is “safe, pure, and potent.”¹⁹

To investigate the use of a stem-cell–based product that is a biologic product in humans, an investigational new drug application that reports data from preclinical studies on the likely safety and efficacy of the investigational product must be filed with the FDA.

To license a biologic product, an application for a biologic license must be approved by the FDA. Such approval requires sufficient data demonstrating that the investigational product is safe and effective in humans.

should be able to address the following questions: Does the donor pose a risk of transmitting infectious or genetic diseases? Does cell or tissue processing pose a risk of contamination or damage? What are the types of cells, and what are the purity and potency of cells in the final product? Will the product be safe and effective in vivo?

DOES THE DONOR POSE A RISK OF TRANSMITTING INFECTIOUS OR GENETIC DISEASES?

Although the use of a person’s own cells and tissues does not require screening and testing for communicable diseases,²⁰ such analysis is required for transplantation between two people.^{21,22} Additional screening and testing are required for certain tissues that pose a particular risk of disease transmission, such as viable leukocyte-rich²³ or reproductive²⁴ cells or tissues.

Gametes “donated by a sexually intimate partner of the recipient for reproductive use”²⁵ and in certain other instances²⁶ are excluded from screening and testing requirements. Thus, in the case of excess embryos from in vitro fertilization (IVF) clinics, which serve as the primary source of human embryonic stem-cell lines, the gametes used to produce those embryos will not have been screened and tested. However, the gamete donors should be screened and tested when pos-

sible; otherwise, the embryos or embryonic stem-cell lines must be tested directly.

Although not required by regulations at this time, it would arguably be beneficial to screen and test donors (or donated tissue) for a predisposition to any serious genetic disease. For example, if the stem cells or embryos carry a single genetic defect known to cause anemia, they are inappropriate for use in hematopoietic reconstitution after radiation treatments. Similarly, if the stem cells or embryos come from a person with a familial history of cardiomyopathy, they may be ill-suited for differentiation into cardiomyocytes.²⁷ Furthermore, if the donor has a family history of a serious disease such as cancer, the recipient risks trading one disease for another. Embryos from known sources, with medical records that can provide information about familial predisposition to medical conditions, are therefore preferred. However, the risks of using stem cells from donors with family histories of serious disease will have to be balanced against eligibility requirements that are so stringent no one can meet them.

In all cases of stem-cell or embryo donation, donor blood samples should be archived so that additional infectious agents and markers of genetic diseases can be identified as appropriate

diagnostic tests are developed. Because years could pass between the donation and clinical use of any subsequently produced stem-cell-based product, donor contact information should be kept current to facilitate rescreening.²⁸ Information linking the cells, tissues, gametes, or embryos to their source must comply with the privacy regulations of the Health Insurance Portability and Accountability Act (HIPAA).²⁹

DOES CELL OR TISSUE PROCESSING POSE A RISK OF CONTAMINATION OR DAMAGE?

The level of concern about potential contamination of and damage to cells and tissues depends on how (and how much) they have been handled and manipulated. Cells removed from a patient and replaced during the same surgical procedure pose no greater risk of disease transmission than the surgery itself. However, the use of products that are “banked, transported, or processed in facilities with other cellular or tissue-based products”¹¹ increases the risk of contamination or damage and may affect the “infectivity, virulence, or other biologic characteristics of adventitious agents in the tissue.”¹¹ Therefore, current good tissue practice³⁰ is required to prevent transmission of communicable diseases and regulations regarding current good manufacturing practice³¹ will apply to stem-cell-based products that require pre-marketing approval. The FDA recently published an interim final rule detailing the compliance requirements for current good tissue practice for phase 1 trials.³²

Standardized procedures for processing and testing will be required for the derivation, expansion, manipulation, banking,³³ and characterization of stem-cell-based products. Each step should be designed with the recognition that exposure and handling of the product at any stage in its manufacture can affect the safety and efficacy of the final product. Furthermore, the ability to trace a given sample of a product back through the manufacturing process to its source will be essential in order to deal with any adverse clinical outcomes. Unlike the testing of chemical pharmaceutical agents, the testing of stem-cell-based products does not fully address all safety concerns because of the inherent complexity of these products.

When stem-cell-based products involve more than minimal manipulation (such as expansion or differentiation), the cells will probably be grown

in culture. This process could involve the use of nonhuman serum, which is often obtained from fetal calves and is therefore a possible source of the prion that causes bovine spongiform encephalopathy. The FDA specifies that fetal-calf serum must come from a country certified to be free of this disease.²⁷

Growth in culture may also involve the use of xenogeneic feeder cells. There has been concern about the potential use of stem-cell-based products derived from human embryonic stem-cell lines in the federal registry, because these lines have all been grown in culture with mouse embryonic feeder cells.³⁴ The FDA has indicated that these lines will not be categorically excluded from transplantation into patients¹³ but they will be subjected to appropriate testing for adventitious agents according to the guidelines for xenotransplantation.⁸ To minimize the risk of transmitting infectious diseases from animals, human embryonic stem-cell lines have been derived from human cells as feeders and human and recombinant serum components.^{35,36} It will still be necessary to screen the human feeder cells for adventitious agents.

Another safety concern is the potential alteration in the genetic makeup of the cells, because stem-cell-based products, particularly those derived from human embryonic stem cells, are likely to require considerable cell expansion, manipulation, and time in culture *ex vivo*. Although karyotypic stability has been demonstrated during the growth of human embryonic stem cells for more than 1 year in culture,³⁷ aberrations in the copy number, mitochondrial DNA sequence, and gene promoter methylation in the long-term passaging of human embryonic stem-cell lines are commonly reported.³⁸ The approach to viral seed-lot systems may prove to be a useful model for controlling genomic stability. Viral seed-lot systems set the permissible number of passages from a well-characterized parental virus through vaccine production. These limits were designed to control the potential for reversion to the virulence of strains that had been attenuated for use in vaccination.³⁹ A similar set of controls on the number of passages, from characterization to testing, of human embryonic stem-cell lines before, during, and after their differentiation into tissues for transplantation would minimize the opportunity for changes in genetic makeup. The genetic and phenotypic characteristics of a line that

exceeded the permissible number of passages would need to be reexamined, and the line might need to be rederived clonally.

WHAT TYPES OF CELLS ARE IN THE PRODUCT AND WHAT ARE THE PURITY AND POTENCY?

The purity of the cell or tissue product to be transplanted is paramount for safety, and the type and potency of the cells or tissues are important factors with respect to efficacy. Table 2 outlines the specific concerns regarding these characteristics that should be addressed before a final stem-cell-based product is tested in humans. In contrast to pharmaceutical products, which can be definitively identified at the end of the manufacturing process with the use of chemical analyses, information about the history of the cells in the stem-cell-based product, the expression pattern of identifying markers, and the function of the cells will all play a role in determining the type of stem cells and the purity and potency of the product.

WILL THE PRODUCT BE SAFE AND EFFECTIVE IN VIVO?

In addition to assessing the safety and efficacy of a stem-cell-based product before transplantation, it is essential to determine where the cells will go and what their functions will be after trans-

plantation. The FDA will probably require proof-of-concept experiments in animal models when little is known about the product, indication, or route of administration.¹³ Determining which animal model is most appropriate and being cognizant of the likely differences between the animal model and the function of the stem-cell-based product in humans will be important.

For some therapies, such as restoring insulin levels in blood, the site-specific integration of the stem-cell-based product is not required for efficacy.⁴³ However, for others, such as repairing the dopaminergic neurons damaged in Parkinson's disease, site-specific integration of cells is essential for a therapeutic effect.⁴⁴ In either case, integrating the cells into a nontarget location could raise questions about safety. Transplanting stem-cell-based products into animals and analyzing whether the cells travel from the site of transplantation and where they functionally integrate will be required to address this concern about site-specific integration.¹³ Biologic distribution studies also will be important. Tagging a stem-cell-based product with markers such as green fluorescent protein or unique surface antigens that can be seen with the use of antibodies may be an effective way to monitor the journey of cells after transplantation. It will also be important to study the longevity of the cells in the stem-

Table 2. Determination of the Cell Type, Purity, and Potency of Stem-Cell-Based Products.

Characteristic	Strategy for Assessment
Cell type ⁴⁰	<p>The types of individual cells and their relative proportions in the stem-cell-based product should be determined by a definitive expression pattern of identifying markers.</p> <p>Fluorescence-activated cell sorting and immunomagnetic separation are techniques that would allow for the isolation of live cells with a particular cell-surface expression profile (positive for desired markers and negative for markers of potential contaminants).</p> <p>The precision of such sorting could be examined by staining a sample of the cells for intracellular markers such as transcription factors.</p> <p>The development of more definitive cell-surface markers that allow for purification of live cells is a critical step in the development of a stem-cell-based product.</p>
Purity ⁴¹	<p>A stem-cell-based product can contain more than one cell type and be "pure." It may be desirable to have a mixture of cell types in the final product.</p> <p>Contaminants of concern include residual stem cells, cells that have differentiated into an undesired cell type during processing, and cells derived from feeder layers. Knowing the history of the cells in the stem-cell-based product will be essential to predict likely contaminants.</p> <p>The inability to detect a cell type in a given stem-cell-based product sample is not a guarantee that the cell type is not there. Therefore, safety studies in animal models will be important.</p>
Potency ⁴²	<p>In vitro demonstration that cells produce insulin in a physiologically appropriate manner, for example, would provide strong evidence that the product is potent.</p> <p>It may be challenging to assess the potency of a stem-cell-based product in vitro because the cells may undergo major functional changes after transplantation; animal models therefore probably will be important for analysis.</p>

cell-based product to determine the likely duration of the therapeutic effect.

Although *in vitro* assays may indicate how the stem-cell-based product is likely to function *in vivo*, studies in animals are needed to monitor the function of the cells after transplantation. Such observations are particularly important for a stem-cell-based product that contains cells that are not terminally differentiated at the time of transplantation. These studies should mimic the route and method of administration to be used in subsequent clinical studies. For example, the transplantation of islet progenitors or islet cells should normalize the concentration of insulin in the blood of diabetic mice, whereas the transplantation of neurons should improve motor coordination in mice with spinal cord damage.

The potential for self-renewal that makes stem cells an attractive source for tissue-replacement therapies also raises concern about tumorigenicity. Investigators should look closely for evidence of the uncontrolled cell growth of the transplanted stem-cell-based product in animal models. Lawrenz et al. have established a highly sensitive animal model that permits the reproducible detection of as few as 20 tumorigenic mouse embryonic stem cells in mice.⁴⁵ An equally sensitive model for detecting undifferentiated human embryonic stem cells would be extremely helpful. Larger numbers of cells will probably be transplanted into humans, so it will be important to determine the level of purity necessary for an acceptable level of risk.

Regardless of whether a stem-cell-based product consists of stem cells, differentiated cells, or a combination of the two, safety requires that differentiation (either *in vitro* before transplantation or *in vivo* after transplantation) occur only along the desired lineages. Animal models will probably be important to examine both the tumorigenicity of the stem-cell-based product and all of the cell types that this product is capable of forming after transplantation.

STEM-CELL-BASED PRODUCTS AND GENE THERAPY

Hypothetically, if stem cells from appropriate tissues were isolated from a person with a disease caused by a single gene mutation, and a functional copy of that gene was introduced into the stem

cells, the transplantation of those replacement cells into the patient would cure the disease. Such an approach would be considered to be gene therapy, because it is a “medical intervention based on modification of the genetic material of living cells.”⁴⁶

In the early 1990s, somatic-cell therapy and gene therapy were often addressed together^{39,46} because many proposals made to the FDA involved the *ex vivo* treatment of somatic cells with a gene-therapy vector and the subsequent return of those modified cells to the patient. This strategy is even more relevant today with the greater possibility of genetically manipulating isolated stem-cell populations in culture. Products containing genetically modified cells to be transplanted into patients are considered to be biologic products requiring pre-marketing approval, and they are subject to the regulations discussed here. Furthermore, viral vectors used to introduce genetic material into a cell also meet the definition of a biologic product⁵ and, if marketed separately from the modified cells, will also be subject to the same regulatory requirements.

Human embryonic stem cells are generated by removing the inner cell mass from a blastocyst and growing the cells in culture. The blastocyst can be formed by means of either IVF or somatic-cell nuclear transfer, in which the nucleus of a somatic cell is combined with an enucleated oocyte. Any product involving embryonic stem cells derived from embryos created by somatic-cell nuclear transfer would be subject to the same regulations applied to other stem-cell-based products in which the cells have been genetically modified (Witten C: personal communication).

CONCLUSIONS

Scientists still have much to learn about determining the safety and efficacy of stem-cell-based products. In particular, the more we know about the biology of self-renewal and differentiation, the more readily the risks of inappropriate cell function can be assessed. In addition, developing techniques to identify cells within a mixed population in culture and to track transplanted cells noninvasively *in vivo* will be critical for ensuring safety.

As new stem-cell-based therapies are developed, the regulatory framework is likely to evolve. Meanwhile, existing regulations pertaining to

biologic products and human cells, tissues, and cellular and tissue-based products provide an appropriate structure for ensuring the safety and efficacy of the next generation of stem-cell-based products. As they conduct research on stem cells, scientists should be aware of the relevant regulations and their likely application to stem-cell-based products.

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