

**PROPOSED APPROACH
TO REGULATION OF
CELLULAR AND TISSUE-BASED
PRODUCTS**

The Food and Drug Administration

February 28, 1997

**PROPOSED APPROACH TO REGULATION OF
CELLULAR AND TISSUE-BASED PRODUCTS**

[Docket Number 97N-0068]

For further information regarding this document, contact:
Sharon Carayiannis
Center for Biologics Evaluation and Research (HFM-630)
Food and Drug Administration
1401 Rockville Pike, Suite 200N
Rockville, MD 20852-1448
301-594-3074

Submit written comments on this document to:

Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Drive, Room 1-23
Rockville, MD 20857

Comments should be identified with the docket number found in the heading of this page.

Submit written requests for additional copies of this document or any other CBER guidance to:

Office of Communication, Training, and Manufacturers Assistance (HFM-40)
Food and Drug Administration
1401 Rockville Pike, Suite 200N
Rockville, MD 20852-1448

Send one self-addressed adhesive label to assist that office in processing your request.

These documents may also be obtained by mail by calling the CBER Voice Information System at 1-800-835-4709 or 301-827-1800, or by fax by calling the FAX Information System at 1-888-CBER-FAX or 301-827-3844.

Persons with access to the INTERNET may obtain these documents using, the World Wide Web (WWW), or bounce-back e-mail. For WWW access, connect to CBER at "<http://www.fda.gov/cber/cberftp.html>". To receive this document by bounce-back e-mail , send a message to "CELLTISSUE@A1.CBER.FDA.GOV".

TABLE OF CONTENTS

Note: Page numbering may vary for documents distributed electronically.

Executive Summary	3
I. Introduction	5
II. Background	5
III. Public health and regulatory concerns associated with cellular and tissue-based products	6
IV. Product factors (tissue characteristics and uses) affecting each area of concern - an overview	7
A) Direct transmission of communicable disease	7
B) Processing concerns	7
C) Clinical safety and effectiveness concerns	8
D) Promotion and labeling	8
E) FDA's baseline knowledge of cell and tissue industry	8
V. The regulatory scheme: product concerns, product characteristics, and uses; required industry actions; and requirements	
A) Direct Transmission of Communicable Disease - Donor Screening, Donor/Product Testing	9
1) Overview	9
2) Regulatory Requirements	9
a) Row A1	9
b) Row A2	9
B) Control of Processing	11
1) Overview	11
2) Factors Affecting Processing Concerns and Clinical Safety and Effectiveness Concerns	12
a) Non-cell/non-tissue components	12
b) Manipulation	13
c) Non-homologous function	15
d) Metabolic function	16

e) Reproductive Function	17
f) Structural Function	17
3) Regulatory Requirements	17
a) Row B1	17
b) Row B2	17
c) Row B3	18
C) Clinical Safety and Effectiveness - Use-specific Concerns	19
1) Overview	19
2) Regulatory Requirements	19
a) Row C1	19
b) Row C2	20
c) Row C3	20
D) Promotion and Labeling	21
E) Monitoring and Education	21
VI. Implementation of Regulatory Procedures	22
A) Stem cells	22
1) Registration and Listing	22
2) Communicable-Disease Screening and Testing	22
3) Processing Standards	23
B) Demineralized bone	24
VII. Conclusion	24
Glossary of Terms as Used in this Document	25

Table 1 Relationships among product concerns, product characteristics, regulatory approaches

Table 2 Regulatory Framework for Cells and Tissue Related Products

PROPOSED APPROACH TO REGULATION OF CELLULAR AND TISSUE-BASED PRODUCTS

February 28, 1997

EXECUTIVE SUMMARY

The Food and Drug Administration is proposing a new approach to the regulation of human cellular and tissue-based products. Tissues have long been transplanted in medicine for widespread uses--such as skin replacement after severe burns, tendons and ligaments to repair injuries, heart valves to replace defective ones, corneas to restore eyesight, and the use of human semen and implantation of eggs to help infertile couples start a family. In recent years, scientists have developed new techniques, many derived from biotechnology, that enhance and expand the use of human cells and tissues as therapeutic products. These new techniques hold the promise of some day providing therapies for cancer, AIDS, Parkinson's Disease, hemophilia, anemia, diabetes, and other serious conditions.

The existing FDA approach to the regulation of human cellular and tissue-based products is highly fragmented. The agency has not previously clearly defined criteria for product characterization, sometimes resulting in confusion on the part of both industry and FDA reviewers. The new regulatory framework, as articulated in this document, would provide a unified approach to the regulation of both traditional and new products. The framework clearly specifies criteria for regulation, and would provide for harmonized review of applications by different Centers within the agency. Additionally, the framework would provide only the degree of government oversight necessary to protect the public health. For products with limited public health concerns, the new framework would allow flexibility and innovation without an application review process.

This new framework would provide a tiered approach to cell and tissue regulation. Regulation would focus on three general areas: 1) preventing unwitting use of contaminated tissues with the potential for transmitting infectious diseases such as AIDS and hepatitis; 2) preventing improper handling or processing that might contaminate or damage tissues; 3) ensuring that clinical safety and effectiveness is demonstrated for 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.

The agency would recommend, but not require, that screening and testing procedures be followed when reproductive tissues are used between sexually intimate partners, and when tissues are transplanted back into the person from whom they were obtained. The agency would require infectious disease screening and testing for cells and tissues transplanted from one person to another (except for reproductive tissues used between sexually intimate partners). The agency would also require that cells and tissues be handled according to procedures designed to prevent contamination and to preserve

tissue function and integrity. In general, there would be no agency submissions required regarding infectious disease controls and handling requirements. Thus, most conventional and reproductive tissues would not be subject to premarket approval requirements. (The agency would impose no requirements on cells and tissues transplanted within a patient's body in a single surgical procedure.)

Cells and tissues that were manipulated extensively, combined with non-tissue components, or were to be used for other than their normal functions would be regulated as biologics or devices requiring premarket approval by FDA. Metabolic cells and tissues, unless minimally manipulated and used for their normal function in the person from whom they were obtained or in close blood relatives of that person, also would be regulated as biologics requiring premarket approval by FDA.

The agency would require that all tissue processing facilities register with the agency, and list their products, via a simple electronic system. And the agency would require that all labeling and promotion be clear, accurate, balanced, and non-misleading.

This new system would provide a rational, comprehensive and comprehensible framework under which tissue processors could develop and market their products. It would ensure that innovation and product development in this rapidly growing medical field could proceed unhindered by unnecessary regulation. At the same time, it would provide physicians and patients with the assurance of safety that the public has come to expect from drugs, biologics, medical devices and other medical products overseen by the FDA.

I. INTRODUCTION

The FDA has formulated a comprehensive approach to the regulation of human cellular and tissue-based products. This approach would provide more appropriate oversight for the wide spectrum of cellular and tissue-based products that are now marketed or envisioned for the future. It would maintain or improve protection of the public and increase public confidence in these new technologies, while permitting significant innovation to go forward unfettered by unnecessary regulatory requirements.

The approach does not encompass vascularized organs or minimally-manipulated bone marrow (both of which are regulated by the Health Resources and Services Administration), transfusable blood products (e.g., whole blood, red blood cells, platelets, and plasma), which the agency already comprehensively regulates,¹ or tissues derived from animals.² It also does not encompass other tissue-related products, such as products used in the propagation of cells or tissues, or that are secreted by or extracted from cells or tissues (e.g. human milk, collagen, urokinase, cytokines, and growth factors.) Such products often raise different manufacturing, safety, and effectiveness issues, and generally are covered by other rules, regulations, and/or standards.

II. BACKGROUND

The term 'tissues' covers a wide range of products used for many medical purposes. In the past, most human tissue used in medicine was comprised of such body components as skin, bone, corneas, and heart valves that were transplanted for replacement purposes, and semen and ova implanted for reproductive purposes. Except for a small number of tissues previously regulated as devices since 1993, FDA's regulation of the conventional tissues used for replacement purposes has focused on preventing the transmission of communicable disease, as authorized by the Public Health Service Act (PHS Act). Three years ago, FDA promulgated interim requirements that such conventional non-

¹ The agency recognizes that it may be desirable to regulate traditional blood products in a manner more like the regulation of other cellular and tissue-based products (to the extent that they present similar issues), and will examine this issue in a future initiative.

² Transplantation of animal tissues into humans (xenograft transplantation) is not addressed in this document, as it raises different public health issues from those raised by transplantation of human tissue into humans. Among other things, the spectrum of infectious agents potentially transmitted via xenograft transplantation is not known, and infectious agents that produce minimal symptoms in animals may cause severe morbidity and mortality in humans. The Public Health Service published a draft Guideline on Infectious Disease Issues in Xenotransplantation in September 1996. (September 23, 1996 Federal Register, 61 FR 49919).

reproductive tissues be tested for HIV and hepatitis and that their donors be screened for risk of infection. FDA has not previously regulated reproductive tissues.

In recent years, scientists have developed innovative methods of manipulating and using human cells and tissues for therapeutic uses. For example, in what is known as somatic cell therapy, scientists are studying the use of human cells that have been manipulated in the laboratory to treat viral infections (including HIV infection), Parkinson's Disease, diabetes, and other diseases and conditions. Other tissue research includes the use of blood from the placental/umbilical cord, to treat diseases or conditions. In general, these forms of cellular and tissue therapy are regulated by FDA as biologics under both the PHS Act and the Federal Food, Drug, and Cosmetic Act (FDCA), with premarketing approval requirements.

III. PUBLIC HEALTH AND REGULATORY CONCERNS ASSOCIATED WITH CELLULAR AND TISSUE-BASED PRODUCTS.

Cellular and tissue-based products and their potential uses are too diverse for a single set of regulatory requirements to be appropriate for all. In an effort to develop a comprehensive scheme that would treat like products alike, but that would establish appropriate regulatory distinctions among cellular and tissue-based products in areas where there were differences, the agency identified the principal public health concerns and attendant regulatory issues associated with the use of these products. Stated as questions, these five overarching public health and regulatory concerns are:

- A) How can the transmission of communicable disease be prevented?
- B) What processing controls are necessary, e.g., to prevent contamination that could result in an unsafe or ineffective product, and to preserve integrity and function so that products will work as they are intended?
- C) How can clinical safety and effectiveness be assured?
- D) What labeling is necessary, and what kind of promotion is permissible, for proper use of the product?
- E) How can the FDA best monitor and communicate with the cell and tissue industry?

With these concerns in mind, the FDA differentiated cells and tissues and their uses by their risk relative to each concern, so as to enable the agency to provide only that level of oversight relevant to each of the individual areas of concern. Thus, under the plan, tissues would be regulated with a tiered approach based on risk and the necessity for FDA review.

IV. PRODUCT FACTORS (TISSUE CHARACTERISTICS AND USES) AFFECTING EACH AREA OF CONCERN - AN OVERVIEW

The agency has identified the following key product factors relating to the above concerns.

A) Direct transmission of communicable disease. The level of public health concern about communicable disease varies depending in substantial part on the following factors: whether the cells or tissues are used in the same person from whom they were obtained (autologous use); whether the cells or tissues are used in a person different from whom they were obtained (allogeneic use); whether they are banked (stored), shipped, or processed in a facility that handles cells and tissues from multiple donors; whether the cells or tissues are minimally, or more-than-minimally, manipulated; whether the tissue is viable or nonviable; and for reproductive cells or tissue, whether they are obtained from a sexually-intimate partner of the transplant/insemination recipient.

B) Processing concerns. The level of concern relating to processing is dependent on the following factors: whether or not the cells or tissues are more-than-minimally manipulated; whether or not they are used for their normal (homologous) function; whether or not they are combined with non-cell/non-tissue components; and whether or not they are used for metabolic function. As will be discussed below in VI B, Control of Processing, products that are more-than-minimally manipulated, or are used for purposes other than their normal function, or are combined with non-cell/non-tissue components, or are used for metabolic function, generally will be subject to more comprehensive regulation of processing than products not characterized by any of these factors, although some exceptions may apply. (For example, use for metabolic function would not in and of itself lead to more comprehensive processing regulation when the product was used in the person from whom it was obtained, or in a close blood relative of that person;³ use of minimally manipulated tissue for other than its normal function may lead to only limited additional regulation of processing, as appropriate to help

³ As a policy matter, the agency would not require investigational use exemptions and premarketing submissions for metabolic cells or tissues that were only minimally manipulated, were to be used for their normal function and were not combined with non-cell/non-tissue components, when those cells or tissues were to be used in the person from whom they were obtained or in a close blood relative of that person. Therefore, FDA would require no agency submissions other than registration, listing, and reporting of adverse events for such products used between close blood relatives. The products would still be subject to appropriate labeling and processing controls.

A close blood relative (also referred to in this document as a family relative) is defined in this document as a first degree blood relative (i.e., parent, child, or sibling). "Unrelated" is used in this document to refer to someone other than a close blood relative of the donor.

ensure intended function). Products not characterized by any of these factors would be regulated under section 361 of the PHS Act, and would not be subject to premarketing requirements. Products characterized by one or more of these factors would be regulated under section 351 of the PHS Act and/or under the FDCA, and generally would be subject to some level of premarketing requirements.

C) Clinical safety and effectiveness concerns. Clinical safety and effectiveness concerns depend on the same factors as do processing concerns (i.e., extent of manipulation; homologous or non-homologous function (that is, whether or not tissue is used for its normal function); combination with non-cell/non-tissue components; and metabolic function). The kinds of information the agency will need to address these concerns may differ depending on whether the cellular or tissue-based product is to be used for a local structural purpose (i.e., reconstruction or repair), a reproductive purpose, or a metabolic purpose. As noted above for processing concerns, and as will be discussed below in section VI C, Clinical Safety and Effectiveness, products that are more-than-minimally manipulated, or are used for non-homologous function, or are combined with non-cell/non-tissue components, or are used for metabolic function, will generally be subject to more comprehensive regulatory controls than products without any of these factors. However, for some products subject to regulation under section 351 and/or the FDCA (see section VI, A, Stem Cells) the agency anticipates establishing product-class-specific processing controls and product standards based on data demonstrating that such controls or standards ensure safety and effectiveness. For these products, applicants would be eligible to certify that these controls and standards have been met in lieu of submitting the underlying data to support such controls and standards.

D) and E) Promotion and labeling and the agency's **baseline knowledge of industry** are cross-cutting issues that apply to all cellular and tissue-based products, with the exception of cells and tissues obtained from and transplanted back into the same person during a single surgical procedure.

V. THE REGULATORY SCHEME: PRODUCT CONCERNS, PRODUCT CHARACTERISTICS AND USES, REQUIRED INDUSTRY ACTIONS, AND REQUIRED REGULATORY SUBMISSIONS.

The agency has developed a chart (Table 1) that outlines the five principal areas of public health or regulatory concern (rows A through E, as described below), the product factors that affect those concerns (and that are the basis for the subdivisions within rows A, B, and C), the industry actions that would be required to address each set of concerns, and the types of required notifications or submissions to the agency. Thus, to determine all the regulatory mechanisms that would apply to any particular product or use, one must look at all the items in the table. The table is provided only as a very short summary of the regulatory approach. As such, it is not intended to stand alone, but to be referred to in conjunction with this document. The following text elaborates on the issues as presented by row in Table 1.

A) Direct transmission of communicable disease - donor screening, donor/product testing.

1) Overview.

Transmission of communicable disease is a concern for all uses of all cellular or tissue-based products. However, the degree of risk, and the appropriate measures to control risk, vary with the source and use of the product. FDA intends to adjust its regulatory approach accordingly.

Row A of Table 1 broadly distinguishes between cellular and tissue-based products for which the agency would not require communicable-disease controls (A1), and products for which it would require communicable-disease controls (A2). A2 is further subdivided according to the kinds of requirements and tests the agency would consider appropriate, based on the source, use, and characteristics of the tissue. Proposals for specific screening, testing, and related requirements for products in these categories are provided in Table 2.

2) Regulatory requirements.

a) Row A1. The agency would not assert any regulatory control over cells or tissues that are removed from a patient and transplanted back into that patient during a single surgical procedure. The communicable disease risks, as well as safety and effectiveness risks, would generally be no different from those typically associated with surgery. Regulated products used in such procedures would continue to be regulated.

b) Row A2. The use of allogeneic rather than autologous cellular or tissue-based products increases the risk of transmission of communicable disease, because the donor from whom the cells or tissue was obtained could carry an infectious agent to which the recipient is susceptible. Also, for both autologous and allogeneic settings, the use of cellular or tissue-based products that are banked, transported, or processed in facilities with other cellular or tissue-based products increases the risk of transmission of communicable disease, because the products are susceptible to contamination or mix-up at each step of such procedures. For example, an infected product could cross-contaminate other cellular or tissue-based products stored in the same liquid nitrogen freezer, or could contaminate processing equipment, which, if not properly treated, could contaminate other tissue processed with that equipment. If contaminated tissue is not properly tested or labeled, health care workers as well as patients may be put at risk.

Therefore, as shown in rows A2b and A2c of Table 1 and in Table 2, the agency intends to require establishments and persons that bank, ship, or process cells or tissues for allogeneic use (except reproductive tissues from sexually intimate partners of the intended recipient of the tissue) to follow specific donor screening and/or donor or product testing and/or product quarantine procedures. Test requirements will differ depending on whether the cells or tissues are nonviable (A2b) or viable (A2c). Viable cells and tissues that are rich in leukocytes (such as stem cells) can harbor human T-cell lymphotropic virus (HTLV) and cytomegalovirus (CMV), and thus would be required to be tested for

those viruses. Viable tissues that are not rich in leukocytes (such as corneas and skin), and nonviable tissues (which do not contain viable leukocytes) would not be subject to HTLV and CMV testing requirements.

In general, the screening and testing would be required to be completed prior to final release of the cells or tissue for transplantation. The establishment or person responsible for determining suitability of release of cells or tissues would be responsible for ensuring that required screening and testing had been performed prior to final release of the material.⁴ For cells or tissue to be obtained from a living donor for allogeneic use, screening and testing would be required prior to collection of the cells or tissue (except in extenuating circumstances).

Additionally, as shown in row A2a of Table 1 and in Table 2, the agency intends to recommend (but not require) that establishments and persons that bank, ship or process cells or tissues from multiple donors for autologous use, or reproductive cells or tissues for reproductive use obtained from sexually intimate partners of the intended recipients of the cells or tissues, also follow the screening and testing procedures prior to collecting the cells or tissue. The agency intends to require that such establishments and persons keep records and label their products as to whether or not recommended donor screening and testing was performed, and if performed, the results obtained. Untested products would be labeled as "untested for BIOHAZARDS."

The screening and testing procedures would be recommended rather than required for such autologous or reproductive uses because 1) autologous use of cells and tissues raises lesser communicable-disease concerns than does allogeneic use; and 2) use of reproductive tissues from sexually intimate partners of intended recipients raises lesser communicable-disease concerns than other allogeneic uses of tissues because the recipient generally will have had prior exposure to the potential risk of receiving communicable disease from that partner. (In contrast, cells or tissue from family-related donors raise the same communicable-disease risks as do cells or tissue from unrelated donors, and consequently family-related donors would be subject to the same testing and screening procedures as are unrelated donors. However, the agency believes that it is appropriate to leave it up to the family and their physician to decide whether to use such tissue, and would not prohibit use even of contaminated material from closely-related donors.)

Cells or tissue from donors who test positive for an infectious disease agent or who have positive risk

⁴ Cells and tissues processed or shipped to a consignee prior to determination of donor suitability would have to be under quarantine, accompanied by records assuring identification of the donor, and indicating that the material had not yet been determined to be suitable for transplantation, insemination, fertilization, further shipment or release. The consignee would be responsible for keeping such material in quarantine, and not shipping it further until donor screening tests had been completed.

factors (that is, whose behavior or experiences could have exposed them to infection) would be required to be labeled 'BIOHAZARD' or "UNTESTED FOR BIOHAZARD" as applicable, and could only be used for transplantation with the documented advance informed consent of the recipient. Autologous tissue from such donors would be required to be labeled 'FOR AUTOLOGOUS USE ONLY.' In those situations in which cells or tissues from such donors are not destroyed, the material could be released from a bank or quarantine only upon documented concurrence of the recipient's physician. Such situations would include cells or tissue to be used in the person from whom it was obtained or in a close blood relative (e.g., autologous stem cells); and reproductive tissue for reproductive use (e.g., semen) from a sexually intimate partner of the intended recipient or from a directed donor; medically necessary and otherwise unavailable cells or tissue (e.g., the tissue is a rare histocompatibility match in a setting where matching is critical).

The agency would engage in rulemaking⁵ under section 361 of the PHS Act to establish procedures and standards for cellular and tissue-based products not subject to premarket requirements under the PHS Act or the FDCA. While under the section 361 rule there would be no required premarketing submissions to the agency concerning communicable-disease testing, the agency would have authority to inspect facilities subject to the requirements, and to take actions to prevent transmission of communicable disease (e.g., orders of retention, recall, and destruction of cellular and tissue-based products).

Cellular and tissue-based products subject to premarket requirements because of processing or clinical attributes (see sections V B and V C below) would still be subject, unless the requirements were unnecessary in a particular situation, to the same core communicable-disease standards and procedures as are cellular and tissue-based products regulated under section 361, and would generally be subject to no additional submission requirements regarding these communicable-disease issues. To the extent that a product requiring premarketing approval were to raise additional communicable-disease concerns as a result of its source, processing, or use, additional standards or procedures could be required in the marketing application⁶ to address these concerns.

B) Control of Processing.

⁵ FDA published an interim rule (21 CFR Part 1270) that contains requirements for communicable disease controls for a subset of cellular and tissue-based products discussed in this document. FDA plans to finalize those requirements, and then engage in further rule making as is necessary, to achieve the purposes of this proposed regulatory scheme.

⁶ For example, manipulation of cells or tissue can affect the infectivity, virulence, or other biological characteristics of adventitious agents in the tissue, thereby increasing communicable-disease risks, and potentially requiring new standards or procedures.

1) Overview.

Row B of Table 1 differentiates products based on whether their characteristics and uses warrant handling and processing controls aimed only at preventing transmission of communicable disease (B2); or warrant processing controls aimed at providing assurance of clinical safety and effectiveness, including but not restricted to preventing transmission of communicable disease (B3). Autologous use of cells and tissues harvested and transplanted in a single surgical procedure would be subject to no FDA oversight (B1). Regulated products used with the cells or tissues or to process the cells or tissues would continue to be regulated.

Improper handling can alter or destroy the integrity or function of cells or tissues. Improper handling also can allow cells or tissues to become contaminated (e.g, bacterial contamination during collection, processing, storage, or transplantation, or cross contamination from other contaminated tissues). Similarly, inadequately-controlled processing can alter or destroy the integrity or function of cells or tissues. Use of cells or tissues contaminated with an infectious agent obviously increases the risk of transmission of communicable disease. Use of cells or tissue with impaired integrity or function also increases the risk of transmission of communicable disease: tissue with impaired integrity or function can lead to transplantation failure, with attendant communicable disease risks (e.g., by increasing the patient's susceptibility to communicable disease, or requiring additional transplantation procedures, with their attendant communicable-disease risks.)

2) Factors Affecting Processing Concerns and Clinical Safety and Effectiveness Concerns.

As previously discussed above, the factors affecting the level of concern regarding processing controls and product safety and effectiveness are: manipulation (i.e., whether the product is minimally or more-than-minimally manipulated); homologous or non-homologous function; whether or not the cells or tissue are combined with non-cell/non-tissue components; and whether or not the product is used for metabolic function as opposed to reproductive or structural function. The agency describes these factors and their regulatory implications below.

(a) Non-cell/non-tissue components. Cellular and tissue-based products may be combinations of cells or tissues with mechanical or synthetic components, with drugs, or with non-cell/non-tissue biologics. The largest and fastest growing class of such combination products are those containing synthetic or mechanical components. These components raise concerns about function, compatibility, and durability. Examples of such combination products would include epithelial cells on a biomatrix to cover burns; allogeneic pancreas cells in a capsule that allows exit of insulin but not entry of antibodies; and bone when combined with collagen or growth factors.

The agency does not anticipate that its planned regulatory approach for cellular and tissue-based products would alter existing agency regulatory policies concerning cellular and tissue-based products containing non-cell/non-tissue components. These combination products are generally subject to

premarketing requirements. The decision as to which part of the agency has primary regulatory responsibility for such combination products will depend on the primary mode of action of the product.

Combination products whose primary mode of action is that of a device are regulated by the Center for Devices and Radiological Health (CDRH). Combination products whose primary mode of action is that of a biologic are regulated by the Center for Biologics Evaluation and Research (CBER). Combination products whose primary mode of action is that of a drug are regulated by the Center for Drug Evaluation and Research (CDER). The agency intends to assure that its reviews of these products are consistently performed, regardless of which Center is responsible for the review.

For combination products with synthetic or mechanical components (which comprise the largest class of combination products), clinical trials and marketing applications must address the clinical safety and effectiveness of the overall product, as well as the function and compatibility of the synthetic or mechanical components. The agency's principal concerns with the use of these materials are that they function correctly, that they last a predictable and adequate length of time, and that they are compatible with surrounding tissue. Clinical trials would thus be required under IND or IDE, as appropriate.⁷

The agency is setting up a Tissue Reference Group to assist in making jurisdictional decisions and applying consistent policy to these products. The agency hopes thereby to resolve expeditiously any scientific or regulatory questions that arise as to where and how such products should be reviewed. The Tissue Reference Group will consist of three CBER and three CDRH employees. It will provide a single reference point for all tissue-related questions received by the Centers or the Office of the Chief Mediator and Ombudsman.

b) Manipulation. The agency would consider processing of structural tissue to be "minimal manipulation" when the processing does not alter the original relevant characteristics of the tissue. The relevant characteristics of structural tissue are those relating to the tissue's ability to carry out the function of reconstruction and/or repair. Thus, separation of structural tissue into components whose characteristics relating to reconstruction and/or repair are not altered would be minimal manipulation. Similarly, extraction or separation of cells from structural tissue, in which the remaining structural tissue's characteristics relating to carrying out reconstruction and/or repair were unaltered, would be considered minimal manipulation. Other examples of procedures that would be considered to constitute only minimal manipulation include cutting, grinding, and shaping; soaking in antibiotic solution; sterilization by ethylene oxide treatment or gamma irradiation; cell separation; lyophilization;

⁷ Tissue-based products that are intended for diagnosis or therapeutic effect by physical action (including reconstruction or repair), and that contain synthetic or mechanical components, and achieve their primary mode of action by means other than metabolic or systemic action, are regulated as devices by CDRH.

cryopreservation; and freezing.

In contrast, extraction of endogenous substances such as minerals or proteins from structural tissue would be considered more-than-minimal manipulation, because such modifications would ordinarily alter the tissue's relevant characteristics.

The agency would consider processing of cells (both structural and non-structural) and non-structural tissues to be "minimal manipulation" when the processing does not alter the biological characteristics of the cells or tissue. The agency would consider processing of cells and non-structural tissues to be "more-than-minimal manipulation" when the processing alters the biological characteristics (and thus potentially the function or integrity) of the cells or tissue, or when adequate information does not exist to determine whether the processing will alter the biological characteristics of the cell or tissue. Examples of more-than-minimal manipulation of cells and tissues include cell expansion, encapsulation, activation, or genetic modification.

Cells or tissues that are more-than-minimally manipulated would be subject to processing controls that generally would cover chemistry, manufacturing, and controls (CMCs), and to premarket requirements for determination of safety and effectiveness because manipulation has the potential, or is intended, to change the cell or tissue's biological characteristics or function. The agency has previously used the concept of manipulation to identify those cellular therapies for which premarket approval would be required. In the somatic cell and gene therapy statement published in October, 1993 (58 FR 53248), the agency stated:

Cells subject to licensure as final biological products when intended for use as cell therapy include cells manipulated in a way that changes the biological characteristics of the cell population...

As described for row B3 in section V B2c below, these products would continue to be subject to CMCs, including process controls and product specifications designed to ensure safety, purity, and potency, and to IND or IDE and marketing application procedures. The agency has prepared CMC guidances for some of these products.

As additional information is generated about procedures in the "more-than-minimal-manipulation" category, the agency intends to consider them to be in the "minimal-manipulation" category when clinical data and experience show that the procedure does not alter the biological characteristics of the cells or non-structural tissue, or the relevant structure-related characteristics of structural tissue. This flexibility will permit product processing that has been found not to affect the pertinent characteristics of the product to be subjected to a lower level of regulation.

In the somatic cell and gene therapy statement, the agency stated that it considered cell selection to

constitute more-than-minimal manipulation. After additional experience and deliberation, the agency now considers cell selection (e.g., selection of stem cells from amongst lymphocytes and mature cells of other lineages) to be minimal manipulation.

In cases where the agency has not made known whether it considers a particular kind of processing to be minimal or more-than-minimal manipulation, individuals may request an opinion from the agency's Tissue Reference Group. Individuals who believe that a particular kind of processing is only minimal manipulation and choose to proceed without seeking clarification assume the risk that they may be out of compliance with premarketing and labeling requirements if the agency determines that the processing is more-than-minimal manipulation.

c) Homologous and non-homologous function. The distinction between homologous and non-homologous function will differ depending on whether or not the product is a structural tissue. The agency considers structural tissue to be used for a homologous function when used to replace an analogous structural tissue that has been damaged or otherwise does not function adequately. Conversely, the agency would consider structural tissue to be performing a non-homologous function when used for a purpose different from that which it fulfills in its native state, or in a location of the body where such structural function does not normally occur.

Examples of homologous uses of structural tissues include bone allograft obtained from a long bone but used in a vertebra; skin allograft obtained from the arm but used as a skin graft on the face; pericardium, a structural covering of the heart, used as a structural covering for the brain; human heart valves; and human dura mater, a fibrous covering of the brain, used as a covering. (Thus, the agency would redesignate human heart valves and human dura mater from devices to tissues subject to section 361 oversight.)

Examples of non-homologous use of structural tissue include amniotic membrane used for wound healing on the cornea, and cartilage placed under the sub-mucosal layer of the urinary bladder to change the angle of the ureter and thereby prevent backflow of urine from the bladder into the ureter. The amniotic membrane, which covers the amniotic sac in utero, would be intended to heal a damaged corneal epithelium by growing new corneal epithelial cells, a function it does not normally perform in utero. The cartilage would be acting as a structural support (its normal function), but in a location where such structural support does not normally exist.

The agency considers cellular products to be used for a homologous function when they are used to perform their native function, and for a non-homologous function when they are used to perform other functions. An example of homologous use would be hematopoietic stem cells used for hematopoietic reconstitution of individuals with marrow aplasia, chemotherapy-induced marrow ablation, Fanconi's anemia, or severe combined immunodeficiency disease. An example of non-homologous use of the same cellular product would be treatment of some adrenal leukodystrophies (which are congenital

metabolic deficiencies), because the sponsor would be intending for the stem cells to perform a metabolic function other than hematopoietic reconstitution.

As for manipulation, the agency would have increased safety and effectiveness concerns for cellular and tissue-based products that are used for non-homologous function, because there is less basis on which to predict the product's behavior. Thus, a tendon used to replace a tendon, even one elsewhere in the body, is still being used for a homologous function and can reasonably be expected to function appropriately. However, without clinical trials, one cannot predict with any certainty how a tendon would act when used for a non-homologous function, such as to constrict a blood vessel to prevent pulmonary embolism.

As described above for manipulation, in cases where the agency has not made known whether it considers a particular use to be homologous or non-homologous, investigators may request an opinion from the agency's Tissue Reference Group. Individuals who believe that a use is homologous and choose to proceed without seeking clarification assume the risk that they may be out of compliance with premarketing and labeling requirements if the agency determines that the use is non-homologous.

d) Metabolic function. Products with a metabolic mode of action usually rely on viable, functioning cells (e.g., pancreatic islet cells, pituitary cells, stem cells) for function. They therefore are sensitive to perturbations and may not retain normal function after the transplantation process. Failure or improper functioning of such products often can have a broad variety of systemic adverse effects, and can be life-threatening (e.g., hematopoietic stem cell replacement after marrow ablation by chemotherapy, pancreatic islet cell therapy for diabetes). Relatively few such products have an established history of safe use. (The agency believes that some autologous and family-related-allogeneic uses of hematopoietic stem cells may have such an established history.)

As noted above, minimally manipulated cellular and tissue-based products with metabolic function raise greater clinical safety and effectiveness concerns than do products with structural or reproductive function. The agency intends to assert premarketing requirements over these products (except when the cells or tissues are used in the person from whom they were obtained or in a close blood relative of the donor, in which case as a policy matter the agency would not require premarket submissions). Thus, for example, the agency would not call for clinical safety and effectiveness information for autologous or family-related allogeneic use of minimally manipulated hematopoietic stem cells (for which no non-homologous use promotional claims were made), but would require clinical safety and effectiveness information for non-family-related allogeneic use of the same cells. As noted in B3 above and section IV below, the agency believes that, for minimally manipulated stem cells used allogeneically to reconstitute the cellular components of blood, sufficient clinical safety and effectiveness data may exist in the near future to enable the development of processing and product standards for certain uses that would obviate the need for applicants to submit CMC and clinical safety and effectiveness information prior to marketing.

e) Reproductive function. In contrast to other metabolic tissues, reproductive tissues raise less substantial issues of rejection, graft versus host disease, or compatibility. Indeed, unlike other tissue, they perform their normal biological functions in an allogeneic setting. Failure of reproductive tissue generally does not have life-threatening or systemic adverse effects except for fertility per se. Reproductive tissues have a long history of use in the medical community. (Assessments of pregnancy success rates for live births in clinics is currently being addressed by the Centers for Disease Control and Prevention, under the Fertility Clinics Success Rate and Certification Act of 1992.)

f) Structural function. Cells and tissues used for structural purposes generally raise different clinical safety and effectiveness concerns than do metabolic cells and tissues. Many structural cellular and tissue-based products raise limited safety concerns beyond adverse local effects. Depending on location, failure of most structural cellular and tissue-based products is unlikely to lead to life-threatening consequences. In many cases, determination of effectiveness of structural therapies is more straightforward than is determination of effectiveness of metabolic therapies.

Additionally, many structural tissue-based products rely predominantly on non-living tissues (e.g., tendons) for function. They therefore usually are relatively insensitive to external factors and are more likely to retain normal function after the transplantation process. Also, many structural tissue-based products are conventional tissues having a long and established history of safe use in the medical community.

3) Regulatory requirements.

a) Row B1. Autologous cells and tissues collected and transplanted in a single surgical procedure (e.g., skin or vein grafts) would not be subjected to any regulatory requirements.

b) Row B2. Cells and tissues not collected from and transplanted into the same person in a single surgical procedure, and not having any of the factors that lead FDA to require section 351 and/or FDCA regulation (i.e., they are minimally manipulated, for homologous use, without non-cell/non-tissue components, and not for metabolic use when from an unrelated donor), would be subject only to handling and processing requirements under section 361 of the PHS Act. The agency intends to promulgate, under section 361, good tissue practice requirements (GTPs) that would be aimed at preventing contamination and preserving product integrity and function through proper handling and processing practices. Apart from registration, listing, and reporting requirements, there would be no required FDA submissions; for example, there would be no premarketing approvals. All establishments or persons that recover, screen, test, procure, bank, process, transport or distribute cells or tissues for allogeneic use or from multiple donors would be subject to some or all of these requirements as appropriate.

Examples of B2 products would include banked tissues, such as semen, human heart valves, powdered

lyophilized non-demineralized bone and other conventional tissues, as well as banked autologous and banked or unbanked family-related allogeneic peripheral and placental/umbilical cord blood stem cells.

c) Row B3. Inadequately controlled or otherwise improper processing can result in products that are ineffective, and in products that are unsafe for reasons other than increasing the risk of transmission of communicable disease. For example, products may be unsafe because they are ineffective (e.g., nonviable stem cells used for hematopoietic reconstitution after chemotherapy) or because they function improperly (e.g., cells or tissue that inappropriately secrete a hormone may cause unwanted metabolic effects). Thus, processing controls for products that raise such clinical concerns often must be more comprehensive than those needed to address risks of transmission of communicable disease.

As discussed in sections IV and V, cellular and tissue-based products that are more-than-minimally manipulated, or are used for non-homologous function, or in combination with non-tissue components, or for a metabolic purpose raise a higher level of processing concerns pertinent to assurance of clinical safety and effectiveness. The agency would subject such products/uses to processing-controls under section 351 of the PHS Act and/or under relevant sections of the FDCA.⁸

Such processing controls generally would cover product chemistry, manufacturing, and controls (CMCs) and be subject to premarket submissions. However, if FDA determines that class-wide standards can be developed such that products in a specified product class are known to be clinically safe and effective when manufactured in accordance with certain defined product specifications and process controls, FDA could establish such standards through rulemaking and require premarketing submission of certification by the applicant that the products met the published standards, rather than a more detailed submission of the clinical data.

For non-family-related allogeneic cord or peripheral blood stem cells for hematopoietic reconstitution, which in some cases have been studied without an investigational new drug exemption (IND), the agency intends to call for a phase in of IND and licensure submissions (see section VI, Implementation of Regulatory Procedures). If, prior to the end of the phase-in period, the agency has received adequate data and information to enable the agency to promulgate standards designed to ensure safety and effectiveness for particular uses of these products, FDA anticipates making a class-specific finding of safety and effectiveness for products meeting those standards (see section V C, Clinical Safety and

⁸ However, as a policy matter, the agency would not subject cells or tissues used for metabolic purposes to such regulation if the cells or tissues were used in the person from which they were obtained or in a close blood relative of the donor, and were minimally manipulated, without non-cell/non-tissue components, and for a homologous function.

Effectiveness, and section VI, Implementation of Regulatory Procedures) . Individuals pursuing licensure subsequent to the adoption of such standards would not have to submit clinical safety and effectiveness data to the agency in their premarketing applications, but would merely have to certify that they meet the standards.

Examples of B3 products used for metabolic function would include hematopoietic stem cells intended for use in recipients who are not close blood relatives of the cell donor or for uses other than to reconstitute the cellular components of the blood; cloned and/or activated lymphocyte therapies for cancer or infectious diseases; and hematopoietic stem cells that have been expanded or modified as part of gene therapy.

Examples of B3 products used for structural function would include demineralized bone (which the agency plans to propose to classify as a class I device and to exempt from premarket submissions), and bone combined with collagen or growth factors.

C) Clinical Safety and Effectiveness - Use-specific Concerns.

1) Overview.

Row C of Table 1 distinguishes products based on whether they have none of the factors relating to clinical safety or effectiveness that would lead FDA to require section 351 or FDCA premarketing submissions requirements (C1); whether they have one or more of such factors and are used to achieve a local structural function (i.e., reconstruction or repair) (C2); and whether they have one or more of such factors and are used to achieve a reproductive or metabolic function (C3).

Products described under C1 would be subject to no section 351 or FDCA requirements for clinical trials demonstrating safety and effectiveness. Products under C2 and C3 would be subject to section 351 and/or FDCA requirements. Requirements for premarket clinical data submissions for C2 and C3 cellular and tissue-based products would generally be as for other regulated products, tailored as appropriate to the characteristics of the product and the concerns raised by the specific indication and product. For serious and life-threatening illnesses, all other applicable policies (e.g., expedited review, treatment IND, accelerated approval) would be available to help speed product availability.

C2 products are separated from C3 products to indicate that in general they would be subject to different safety and effectiveness endpoints to fulfill clinical trial requirements. Clinical trial requirements for C2 products (whether regulated as biologics or devices) would generally be consistent with those for devices for the same indication, whether regulated under INDs or IDEs (investigational device exemptions). Clinical trial requirements for C3 products would generally be consistent with those for new drugs or biologics for the same indication.

2) Regulatory Requirements.

a) Row C1. FDA would not require premarket review and approval for

cellular and tissue-based products that are minimally manipulated, are used for homologous function, do not contain non-cell/non-tissue components, and are for structural or reproductive use. Such products raise relatively limited clinical safety and effectiveness concerns, and thus would not be subject to premarket submission of clinical data. Additionally, as a policy matter the agency would not require premarket submission of clinical data for cellular or tissue-based products that are minimally manipulated, are used for homologous function, do not contain non-cell/non-tissue components, and are for metabolic use, when they are to be used autologously or in a close blood relative of the donor. Communicable-disease risks would be addressed under section 361 as discussed above in sections VI, A, 2, and VI, B, 2.

Examples of such products would include heart valve and dura mater transplants, vein grafts, tendons to repair or replace tendons, autologous or family use of peripheral or cord blood stem cells for hematopoietic reconstitution, and human gametes (sperm and eggs), zygotes, and embryos intended for insemination, fertilization, or transfer.

b) Row C2. The agency recognizes that cellular and tissue-based products for structural use raise different safety and effectiveness issues than do products for metabolic or reproductive use, and that they can be evaluated in a manner generally consistent with that of devices for the same indication, modified as appropriate for the nature of the product. (They may also be classified as devices). The agency outlined its approach for evaluating a major subset of such products in the May, 1996 Guidance on Applications for Products Composed of Living Autologous Cells Manipulated Ex Vivo and Intended for Structural Repair or Reconstruction (MAS Cells) and the CMC Guidance for Autologous Cell Therapy (1997).

The agency recognizes that many of the highly manipulated cellular and tissue-based products intended for structural purposes often will be used for the same indication as are some devices, or will be classified as devices. It is the intent of CBER and CDRH to ensure consistent review of such products, whether regulated as devices or biologics, and to establish clinical effectiveness standards for structural cells regulated as biologics that would be consistent with those existing for comparable devices. However, different products may raise different safety, effectiveness, or durability concerns, and may be amenable to different methods for measuring outcomes.

Some examples of C2 cellular and tissue-based products include manipulated cells for autologous structural use (MAS cells) such as expanded chondrocytes to repair damaged knee cartilage, and devices such as demineralized bone. (The agency does not intend for demineralized bone used alone to be subject to premarket submission requirements. The agency plans to propose to classify demineralized bone as a class I device and to exempt it from premarket submissions, as described in section VI.)

c) Row C3. Some examples of C3 cellular products include autologous

genetically-manipulated cellular therapies involving correction of genetic defects, non-family-related allogeneic cord or peripheral blood stem cells, stem cell therapies involving growth factors such as interleukin-3 and stem cell factor or gene therapy, activated lymphocytes for treatment of cancer, and cloned lymphocytes for the treatment of HIV infection or other infection. (See section VI A below regarding phase-in of licensure requirements for non-family-related allogeneic cord and blood stem cells.)

D) Promotion and Labeling. Row D of table 1 addresses the issue of potentially false or misleading claims. For cellular and tissue-based products regulated under section 361, labeling would need to be clear, accurate, balanced, and non-misleading. Such labeling could include what the tissue is and how it has been processed; the homologous uses of the tissue; and the communicable-disease screening, testing and quarantine procedures that were followed and results obtained. FDA intends to propose regulations to address labeling requirements under section 361 of the PHS Act.

Products that are intended or promoted for use for a non-homologous function would fall outside the scope of the section 361 regulation the agency intends to promulgate, and would be subject to regulation as biological drugs or devices under section 351 of the PHS Act and/or the FDCA. For cellular and tissue-based products regulated under FDCA and/or section 351 of the PHS Act, the agency intends to regulate labeling under existing authorities therein.

E) Monitoring and Education. At present, FDA does not know the full size and scope of the cell and tissue industry and its potential products. The agency believes that, in order for it to understand the issues raised by these new products and be able to educate the industry and keep it up to date regarding FDA policies, guidances, and requirements, as well as to enable the agency to inspect establishments for compliance with applicable laws and regulations, all establishments that recover, screen, test, procure, bank, process, transport or distribute cells or tissues from multiple or allogeneic donors, should register and list their products with FDA. Therefore, the agency would require registration and listing for all such establishments and products over which FDA is asserting its jurisdiction under section 361 of the PHS Act, section 351 of the PHS Act, or the FDCA. The agency is developing a simple electronic filing system that it will use for establishment registration and product listing. Registration and listing for products subject to section 361 oversight would not be required until the electronic system is in place.

FDA does not intend to require that it be sent reports of errors and accidents that occur during processing and distribution of cellular and tissue-based products subject to section 361 controls. However, as part of the GTP requirements, establishments and persons will be required to identify and investigate errors and accidents, take appropriate corrective action, and maintain records of such failure assessments. The agency does intend to propose post-market adverse event reporting requirements relating to transmission of communicable disease.

The agency intends to apply registration and listing requirements in section 510 of the FDCA as well as existing post-market reporting requirements to those cellular and tissue-based products subject to regulation under section 351 of the PHS Act and/or the FDCA. The agency intends to propose regulations for registration, listing, GTPs, and post-market adverse event reporting of those cellular and tissue-based products regulated under section 361 of the PHS Act.

VI. IMPLEMENTATION OF REGULATORY PROCEDURES

The agency intends to implement this regulatory plan in a step-by-step fashion. The agency intends to promulgate through notice and comment rule-making new regulatory requirements, and to allow for phase-in as appropriate. Some examples of how FDA intends to implement this regulatory plan for selected products are as follows.

A) Stem cells. The agency intends to phase in its regulatory oversight of minimally manipulated hematopoietic stem cells derived from cord or peripheral blood and used for hematopoietic reconstitution in patients who are not close blood relatives of the donors from whom the cells were obtained. (Minimally manipulated hematopoietic stem cells to be used for their normal function in the person from whom they were obtained or in a close blood relative would be regulated under section 361, and would not be subject to premarket application requirements.) The agency intends to phase in regulation of allogeneic use of these products as follows.

1) Registration and Listing. FDA intends that all facilities that recover, screen, test, procure, bank, process, transport or distribute stem cells, derived from umbilical cord blood or peripheral blood, to treat, cure, diagnosis, or mitigate diseases in humans, be required to register with the FDA and list the products at their facility. Registration and listing would be accomplished through an electronic system that the agency is developing.

2) Communicable-Disease Screening and Testing. The agency intends to require testing of blood samples from allogeneic donors of hematopoietic stem cells in order to prevent the transmission of communicable diseases. For peripheral blood stem cell donors, the donor's blood, and for umbilical cord blood donors, the mother's blood, would be required to be tested for HIV, cytomegalovirus, HTLV, syphilis and hepatitis infection (i.e., HBsAg, anti-HIV-1, anti-HIV-2, HIV-1-Ag, anti-HTLV-I/II, anti-HCV, a serologic test for syphilis, and anti-CMV). The medical history and physical examination of prospective donors would include screening for high risk for HIV and hepatitis, Creutzfeldt Jacob Disease (CJD), and tuberculosis.

The agency intends to recommend, but not require, that testing be performed when the stem cells will be used in the person from whom they were obtained. In such case, the agency would recommend only the following tests: HBsAg, anti-HCV, anti-HIV-1, anti-HIV-2, HIV-1-Ag, and anti-HTLV-I/II. The agency also would recommend that the history and physical examination of the donor include screening

for high risk for HIV and hepatitis. The agency would require that record-keeping and labeling reveal which of the recommended tests were performed, and the results obtained from those tests, as well as which of the recommended tests were not performed. Appropriate labeling would be as follows: 'tested and negative', 'tested and positive', or 'not tested for biohazards.'

Ordinarily, cells or tissue would not be collected from a donor testing positive for any of these viruses, and if collected would be required to be destroyed. However, the agency recognizes that there may be circumstances justifying storing or using such cells or tissues. For example, in cases where a stem cell donor tests positive for a virus or has been found to be at risk of infection (even if testing negative), and the stem cells are intended for autologous use, for use in a close blood relative, or for use in a transplant recipient with a rare histocompatibility match, the agency intends to require that 1) the cells be labeled "BIOHAZARD", 2) autologous products also be labeled "FOR AUTOLOGOUS USE ONLY", 3) written advanced informed consent of the recipient be documented, and 4) there be documented concurrence of the recipient's physician before the cells could be released from a cell bank.

3) Processing Standards. The agency intends to promulgate establishment controls, processing controls, and product standards under section 351 of the PHS Act. For minimally manipulated stem cells used for hematopoietic reconstitution, the agency believes that it may be possible to develop product standards (including manufacturing controls and product specifications aimed at ensuring product safety and efficacy) from existent published clinical trial data or data developed in the near future. FDA intends to invite professional groups and individuals to submit to the agency data and standards that they believe would ensure safety and effectiveness. If sufficient data are not available to develop processing and product standards after a specified period of time, the stem cell products would be subject to IND and marketing application requirements.

FDA intends to list in the Federal Register relevant questions for developing the data and standards, and the deadline for submission of responses. Examples of the kind of information that the agency believes will be necessary to have in standards include criteria for acceptance of a unit (such as volume, storage temperature limits, limits on microbial or other contamination, viable cell number, and functionality), and procedures for handling, transporting, storing, and thawing materials, and for when and how contamination and viability testing should be carried out.

Upon development and promulgation of standards designed to ensure safety, purity, and potency, FDA would issue licenses based on a certification by the applicant that the standards are met. The certification could be made in the same submission as the registration and listing. FDA would issue a license based on the certification submission.

During the interim period, FDA would not call for licensure of such products for unrelated allogeneic use, but would require establishment registration and product listing. The agency also could perform inspections for applicable GMP compliance, and could take enforcement action against facilities as

needed (for example, because of lack of appropriate communicable disease-testing).

B) Demineralized bone. FDA would consider demineralized bone (decalcified freeze dried bone allograft) to be an unclassified pre-Amendments device rather than a tissue under section 361 because the bone is more-than minimally manipulated.⁹ FDA would seek a classification recommendation from the Orthopedic/Dental Advisory Panels. The device to be classified would be defined as including allograft bone that is processed ONLY to demineralize and preserve the bone, and ONLY intended to be used as a bone filler in orthopedic and/or dental procedures.

Based on current information, FDA expects to propose that demineralized allograft bone be regulated as a Class I medical device exempted from premarket notification. In addition, FDA expects that it would also propose to exempt demineralized allograft bone from the GMP requirements except for certain requirements consistent with those proposed for human tissues regulated under section 361.

To ensure that the GMP requirements applicable to demineralized bone are ultimately consistent with the requirements for human cellular and tissue-based products regulated under section 361, the Federal Register documents regarding the requirements for each would be published as companion documents.

VII. CONCLUSION

The agency believes that the above-described proposed approach to the comprehensive regulation of cellular and tissue-based products would provide adequate protection of public health, both from the risks of transmission of communicable disease and from the risks of therapies that may be dangerous, while enabling investigators to develop new therapies and products with as little regulatory burden as possible. The agency intends for this regulatory scheme to encourage research and innovation, while at the same time set boundaries between the kinds of experimentation with human products that warrant only minimal FDA oversight and the kinds of experimentation with human products that warrant greater FDA oversight.

⁹ In contrast to how it would regulate demineralized bone, FDA would regulate powdered bone (freeze dried bone allograft) under section 361 (falling in rows B2a and C1 of Table 1), because the bone is only minimally manipulated - the processing does not change the integral structure of the bone.

GLOSSARY OF TERMS AS USED IN THIS DOCUMENT

ablation	Removal or destruction
allogeneic use	Cells or tissue transplanted from one person to another.
autologous use	Cells or tissue removed from and transplanted back into the same person.
close blood relative	A first degree blood relative (i.e., parent, child, or sibling).
cord blood	Blood in the placenta and umbilical cord, e.g., blood taken at the time of birth
family relative	A first degree blood relative (i.e., parent, child, or sibling).
hematopoietic	Giving rise to the cellular elements of the blood (e.g., white blood cells, red blood cells, platelets).
hematopoietic Stem cells	Cells capable of generating white blood cells, red blood cells, and platelets. For the purposes of this document, these would include progenitor cells that are committed to develop into a particular cellular lineage. Hematopoietic stem cells presently can be collected (as a very small fraction of the cells) from peripheral blood, placental/umbilical cord blood, and bone marrow, often for transplantation into patients whose own hematopoietic stem cells have been destroyed by anticancer treatment or disease
homologous function	Use for the normal function of the cell or tissue, and, for structural tissue, use for a structural purpose in a location of the body where such functional purpose normally occurs (see P. 15).
MAS cells	<u>M</u> anipulated <u>A</u> utologous cells for <u>S</u> tructural use
metabolic use	For systemic effect.

minimal manipulation	Processing that does not alter the biological or relevant functional characteristics of cells or tissue (see P. 13).
more-than-minimal manipulation	Processing that alters the biological or relevant functional characteristics of cells or tissue (see P. 13).
non-homologous function	Use for other than the normal function of the cell or tissue, or for structural tissue, use for a structural purpose in a location of the body where such functional purpose does not normally occur (see P. 15).
peripheral blood	Circulating blood (in contrast to, for example, blood in bone marrow)
reproductive tissue	Semen, ova, embryos.
reproductive use	To treat infertility.
stem cells	Cells capable of replicating themselves and of generating more-differentiated daughter cells.
structural use	For anatomic reconstruction or repair.
unrelated	Someone other than a close blood relative.

RELATED PRODUCTS

PROPOSAL FOR SPECIFIC COMMUNICABLE DISEASE CONTROLS¹

	Testing ²										Screening			Quarantine ³
	HIV	HCV	HBV	HTLV	CMV	Treponema pallidum	Chlamydia trachomatis	Neisseria gonorrhoea	High risk for HIV & Hepatitis	CJD screens ⁵	TB screen			
2a Autologous Banked Tissue														
Stem Cells	R	R	R	R						R				
Other Autologous Tissue	R	R	R							R				
2b Allogeneic, Nonviable Tissue	X	X	X			X				X	X	X		R
2c Allogeneic, Viable Tissue														
Stem cells from Family-related donors	X	X	X	X	X	X				X	X	X		
Reproductive Tissue from Sexually Intimate Partners	R	R	R	R	R	R	R	R		R	R	R		
Other Reproductive Tissue (including directed donors)	X	X	X	X	X	X	X	X		X	X	X		X
Other allogeneic Viable Tissue ⁴	X	X	X	X	X	X				X	X	X		R

Legend:

X-required

R-recommended, for tests; labeling as: 'tested/negative', or 'not tested for biohazards' will be required.

notes:

¹Banked tissue for autologous use, from allogeneic family-related donors, from directed reproductive tissue donors, from sexually intimate partners, or in cases where there is a documented urgent medical need from a donor who has a positive risk factor and/or tested positive for an infectious disease agent, will not be required to be destroyed if:

- a) the product is labeled 'BIOHAZARD' or 'untested for BIOHAZARDS', as applicable
- b) autologous tissue is labeled 'FOR AUTOLOGOUS USE ONLY'
- c) written advance informed consent of the recipient is documented
- d) there is documented knowledge and authorization of the recipient's physician

Tissue unsuitable for transplantation may be used for non-clinical research purposes if labeled 'BIOHAZARD' or 'untested for BIOHAZARDS', and 'FOR RESEARCH USE ONLY'

²For autologous or allogeneic cord blood donors, a mother's sample may be used for screening and testing.

³For allogeneic tissue that can be stored, quarantine for six months pending retesting of the donor will be required for all reproductive tissue, excluding sexually intimate partners. For other banked tissue and cells from living donors, quarantine for six months pending retest of the donor, or of the mother will be recommended, where appropriate and feasible, not required.

⁴Requirements for HTLV and CMV testing only apply to leukocyte rich tissue (e.g. stem cells); they will not apply to cornea or skin donors.

⁵For dura mater donors, in addition to history for risk factors, a gross and histological examination of brain tissue will also be required.

Table 1

Relationships among product concerns, product characteristics, regulatory approaches

Product Concern	Product Characteristic (Product Factors)	Industry Action Required	Regulatory Submission
<p>A. Direct transmission of communicable disease (e.g., donor screening and testing)</p>	<p>1. SURGERY (Cells or tissue are removed from and transplanted back into the same person in a single surgical procedure)</p> <p>2a. AUTOLOGOUS banked/processed/shipped; REPRODUCTIVE from sexually intimate partner</p> <p>2b. ALLOGENEIC, nonviable tissue</p> <p>2c. ALLOGENEIC, viable tissue</p>	<p>1. None.</p> <p>2a. Screening, testing recommended; other GTPs would be required, e.g., recordkeeping, labeling, product tracking, recalls, notification of communicable disease transmission.</p> <p>2b, 2c. GTPs would be required e.g., screening, testing, recordkeeping, labeling, product tracking, recalls, notification of communicable disease transmission.</p>	<p>1. None</p> <p>2a 2b 2c. No FDA submission. Requirements would be set in new final rule for allogeneic tissue-related products under section 361 (finalization of the interim final rule), and in rulemaking under sections 361 and 351 which would add more products and more specific testing requirements.</p>
<p>B. Control of Processing</p> <p>Improper handling or inadequately controlled processing may result in product contamination and consequent communicable disease transmission;</p> <p>or in failure to preserve product integrity and function, and consequent enhanced susceptibility to communicable disease;</p> <p>or in failure to preserve product integrity and function with resulting unsafe or ineffective products.</p>	<p>1. SURGERY (Cells or tissue are removed from and transplanted back into the same person in a single surgical procedure.)</p> <p>2. MINIMALLY MANIPULATED & homologous function & no non-tissue components, and structural, reproductive, or autologous/related-allogeneic metabolic</p> <p>3. MORE-THAN-MINIMALLY MANIPULATED or non-homologous function or non-tissue components or unrelated metabolic</p>	<p>1. None</p> <p>2. GTPs relating to contamination, integrity and function.</p> <p>3. Would have to follow GMPs and have stricter processing controls encompassing clinical safety and effectiveness concerns.</p>	<p>1. None</p> <p>2. No FDA submission regarding processing. Requirements would be set in rulemaking under section 361.</p> <p>3. A marketing application would ordinarily be required to contain a CMC section. If determinations are made that the safety and effectiveness of a product category can be assured by meeting product specifications and processing controls, then applicants would need only to submit a certification that they meet the product specifications and processing controls.</p>

Table 1 (continued)

<p>C. Clinical safety (not restricted to communicable-disease risks); clinical effectiveness (including use-specific concerns).</p> <p>Attributes of importance are:</p> <p>a) more than minimal manipulation;</p> <p>b) non-homologous use;</p> <p>c) combination with non-cell/non-tissue components;</p> <p>d) metabolic use (other than reproductive) except when used autologously or in a close family member.</p>	<p>1. Product is without any of factors a, b, c, or d.</p> <p>2. Product is for local, structural reconstruction or repair and has factors a, b, or c.</p> <p>3. Product is for reproductive or metabolic use with factors a, b, c, or d.</p>	<p>1. None.</p> <p>2. Would have to gather clinical safety and effectiveness data.</p> <p>3. Would have to gather clinical safety and effectiveness data.</p>	<p>1. No FDA submission.</p> <p>2. Studies would have to be done under IND or IDE; Marketing application would have to be submitted (BLA, 510(k) or PMA); standard for determination of effectiveness would be consistent with that for devices. Standards for manipulated autologous structural cells would be as described in MAS cell policy guidance.</p> <p>3. Studies would have to be done under IND; marketing application would have to be submitted (BLA); standard for determination of effectiveness would be consistent with that for biologics.</p>
<p>D. Promotion and labeling</p>	<p>All cellular and tissue-based products (excluding cells and tissues that are removed from and transplanted back into the same person in a single surgical procedure).</p>	<p>Clear, accurate, balanced and non-misleading labeling</p>	<p>No FDA submission concerning labeling for products regulated only under section 361 (providing claims are limited to those within homologous use). For products regulated under section 351 or as a device, the usual rules would apply concerning labeling.</p>
<p>E. Baseline Knowledge of Industry</p>	<p>All cellular and tissue-based products (excluding cells and tissues that are removed from and transplanted back into the same person in a single surgical procedure).</p>	<p>Notification of FDA</p>	<p>Registration and listing under new regulation under 361 or under sec. 510 of the FDC Act.</p>

PROPOSED NEW REGULATORY FRAMEWORK FOR HUMAN TISSUE

CONCERN 1: DISEASE TRANSMISSION (Does the Tissue Pose a Risk of Transmitting Diseases Such as AIDS or Hepatitis?)

Product Characteristic	Industry Action Required	Submission to FDA
Tissue transplanted within one person during a single surgical procedure	None	None
Tissue transplanted within one person that has been banked, processed, or shipped	Disease screening and testing recommended; Good Tissue Practices (GTPs) (handling, recordkeeping, and labeling procedures) would be required	None
Tissue donated from one person to another	Subject to GTPs; disease screening and testing would be required	None

CONCERN 2: CONTROL OF PROCESSING
(What Kinds of Handling and Processing Controls Would Be Necessary?)

Product Characteristic	Industry Action Required	Submission to FDA
Tissue transplanted within one person during a single surgical procedure	None	None
Minimally processed structural ³ tissue used for its normal function and having no nontissue parts; or reproductive tissue ⁴ used for its normal function, and having no non-tissue parts	Would be subject to GTPs relating to contamination, integrity, and function	None
Minimally processed metabolic tissue ⁵ transplanted into the same person, or into a family member, used for its normal function, and having no nontissue parts	Would be subject to GTPs relating to contamination, integrity, and function	None
Metabolic tissue transplanted to another person not related to the donor; or that has been manipulated, or is used for other than its normal function, or has nontissue parts	Would have more comprehensive processing controls than GTPs (to address clinical safety/effectiveness concerns)	Human testing exemptions and marketing approval by FDA would be required. (In certain cases, certification to standards may substitute for data submission.)
Structural tissue that has been manipulated, or is used for other than its normal function, or has nontissue parts	Would have more comprehensive processing controls than GTPs (to address clinical safety and effectiveness concerns)	Human testing exemptions and marketing approval by FDA would be required.

³ Structural tissue comprises such tissue as corneas, ligaments, bones, cartilage, tendons, dura mater, and heart valves.

⁴ Reproductive tissue comprises such tissue as ova, semen, and embryos.

⁵ Metabolic tissue is tissue that affects the function of the entire body (e.g., umbilical cord stem cells infused into a patient to reconstitute the cellular elements of the patient's blood, or pancreatic islet cells implanted to treat diabetes).

CONCERN 3: CLINICAL SAFETY
(Does the Product Need FDA Approval for Safety/Effectiveness?)

Product Characteristic	Industry Action Required	Submission to FDA
<p>Minimally processed structural tissue used for its normal function, and without nontissue parts; or metabolic tissue that is used in the same person or in a close relative of the donor that is minimally processed, used for its normal function, and has no nontissue parts.</p>	<p>None</p>	<p>None</p>
<p>Tissue used for structural reconstruction or repair that: 1) has been manipulated; or 2) is used for other than its normal function; or 3) is combined with nontissue parts</p>	<p>Would have to gather clinical safety and effectiveness data</p>	<p>Human testing exemptions and marketing approval required; standard for effectiveness determination would be consistent with that for comparable devices</p>
<p>Metabolic tissue used in a person not related to the donor, or that: 1) has been manipulated; or 2) is used for other than its normal function; or 3) is combined with nontissue parts</p>	<p>Would have to gather clinical safety and effectiveness data</p>	<p>Human testing exemptions and marketing approval by FDA required; standard for effectiveness determination would be consistent with that for biologics</p>
<p>Reproductive tissue that is: 1) manipulated; 2) used for other than its normal function; or 3) combined with nontissue parts</p>	<p>Would have to gather clinical safety and effectiveness data</p>	<p>Human testing exemptions and marketing approval by FDA required; standard for effectiveness determination would be consistent with that for biologics.</p>

**CONCERN 4: CLAIMS MADE BY MANUFACTURERS
(What Regulation Is Needed of Product Labeling and Advertising?)**

Product Characteristic	Industry Action Required	Submission to FDA
Tissue transplanted within one person during a single surgical procedure	None	None
All other tissue	Clear, accurate, balanced, and nonmisleading labeling and promotion	No FDA submission concerning labeling for products regulated only under section 361; for products regulated under section 351 and/or FDC Act, normal rules would apply

**CONCERN 5: BASELINE KNOWLEDGE OF INDUSTRY
(Should Tissue Products Be Registered with FDA?)**

Product Characteristic	Industry Action Required	Submission to FDA
Tissue transplanted within one person during a single surgical procedure	None	None
All other tissue	Notification of FDA	Registration and listing under new regulation under 361 or under section 510 of the FDC Act