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Part II

**Department of
Health and Human
Services**

Food and Drug Administration

**Application of Current Statutory
Authorities to Human Somatic Cell
Therapy Products and Gene Therapy
Products; Notice**

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 93N-0173]

Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is making available, through this document, a statement of the manner in which FDA's current statutory authorities governing therapeutic products apply to human somatic cell therapy products and gene therapy products. FDA is publishing this statement in response to requests that the agency clarify its regulatory approach and provide guidance to manufacturers of products intended to be used in somatic cell therapy or gene therapy. As scientific knowledge in the area of somatic cell and gene therapy continues to accumulate and evolve, the agency's approach may also evolve.

DATES: Submit written comments on the document by December 13, 1993.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857. Submit investigational new drug applications (IND's) for somatic cell therapy and gene therapy products to the Division of Application Review and Policy (HFM-585), Office of Therapeutics Research and Review, Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448. Submit written requests for single copies of the document entitled "Points to Consider in Human Somatic Cell Therapy and Gene Therapy" to the Congressional and Consumer Affairs Branch (HFM-12), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448, 301-295-9000. Send two self-addressed adhesive labels to assist that office in processing requests.

FOR FURTHER INFORMATION CONTACT: Ann Reed Gaines, Center for Biologics Evaluation and Research (HFM-635), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448, 301-594-3074.

SUPPLEMENTARY INFORMATION:

I. Introduction

As a consequence of scientific and biotechnological progress during the past decade, new therapies involving somatic cells and genetic material are being investigated, and commercial development of products for use in somatic cell therapies and gene therapies is occurring. Existing FDA statutory authorities, although enacted prior to the advent of somatic cell and gene therapies, are sufficiently broad in scope to encompass these new products and require that areas such as quality control, safety, potency, and efficacy be thoroughly addressed prior to marketing. Manufacturers and other interested parties have questioned FDA regarding how such products will be regulated. This statement outlines the current regulatory approach to products intended for use in somatic cell and gene therapies.

II. Background

A. Legal Authorities

FDA regulates numerous kinds of products intended to prevent, treat, or diagnose diseases or injuries under legal authorities established in the Public Health Service Act (the PHS Act) and the Federal Food, Drug, and Cosmetic Act (the act). Section 351(a) of the PHS Act (42 U.S.C. 262(a)) identifies a biological product as "any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or its derivatives (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of diseases or injuries of man." Section 201(g)(1) of the act (21 U.S.C. 321(g)(1)) defines the term "drug," in part, as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals." The term "device" is defined in section 201(h) of the act, in part, as: "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article * * * intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, * * * which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes." Both the "drug" definition and the "device" definition also include articles "intended to affect the structure or any function of the body."

Section 351(a) of the PHS Act requires premarket approval for biological

products. Licenses are to be issued upon a showing that the establishments and products "meet standards, designed to insure the continued safety, purity, and potency of such products * * *" (42 U.S.C. 262(d)). A biological product's effectiveness for its intended uses must be shown as part of the statutory requirement for potency (21 CFR 600.3(s)). At the investigational stages, when the products are being studied in clinical trials to gather safety and effectiveness data, biological products must meet the requirements of part 312 (21 CFR part 312). FDA's biologics regulations require the submission of both product license applications (PLA's) and establishment license applications (ELA's) (21 CFR 601.1 through 601.10). Biologics establishments and products must satisfy detailed standards set forth in the regulations (21 CFR parts 600 through 680).

Section 351(b) of the PHS Act prohibits falsely labeling or marking a biological product. Under section 361 of the PHS Act (42 U.S.C. 264), the agency may promulgate regulations to prevent the introduction, transmission, or spread of communicable diseases.

Products considered to be biological products subject to the provisions of section 351 of the PHS Act are simultaneously also drugs or devices subject to the applicable provisions under the act. For example, the adulteration, misbranding, and registration provisions of the act would apply to the product as a drug or device.

Under section 501 of the act (21 U.S.C. 351), both drugs and devices are considered adulterated for any of a number of specified reasons. Included among these adulteration provisions is the requirement that the methods and facilities and controls used for manufacture, processing, packing, and holding or installation conform with current good manufacturing practice (CGMP) regulations (21 U.S.C. 351(a)(2)(B) and (h)). FDA's implementing regulations codified at 21 CFR parts 211 and 820 specify the drug and device CGMP requirements.

Section 502 of the act (21 U.S.C. 352) sets forth misbranding provisions that apply to drugs and devices. Among other circumstances, a drug or device is considered misbranded if the labeling is false or misleading or if the labeling fails to bear adequate directions for use or adequate warnings against unsafe use (21 U.S.C. 352(a) and (f)). Any drug or device is also misbranded if it is dangerous to health when used in the manner or with the frequency suggested in the labeling (21 U.S.C. 352(j)). For prescription drugs and restricted

devices, section 502 of the act describes certain information that must be included in all advertisements or other printed material (21 U.S.C. 352(n) and (r)). FDA's regulations also establish labeling and advertising requirements in more detail (21 CFR parts 201, 202, and 801).

Section 510 of the act (21 U.S.C. 360) requires persons who own or operate establishments for the manufacture, preparation, propagation, compounding, or processing of drugs or devices (with certain exceptions) to register those establishments with FDA. Individuals who must register their establishments under section 510 of the act must also file a list of all the drugs and devices being made or processed at the establishment. FDA's registration regulations are codified at 21 CFR parts 207 and 807.

Although products regulated by FDA as biological products must also meet drug or device requirements, the agency does not require duplicate premarket approvals. For example, if FDA requires a PLA to be submitted for the product as a biologic, the agency does not also require submission of a new drug application (NDA) or a device premarket approval application (PMA).

The interstate commerce nexus needed to require premarket approval under the statutory provisions governing biologics and drugs may be created in various ways in addition to shipment of the finished product by the manufacturer. For example, even if a biological drug product is manufactured entirely with materials that have not crossed State lines, transport of the product into another State by an individual patient creates the interstate commerce nexus. If a component used in the manufacture of the product moves interstate, the interstate commerce prerequisite for the prohibition against drug misbranding is also satisfied even when the finished product stays within the State. Products that do not carry labeling approved in a PLA (or NDA) are misbranded under section 502(f)(1) of the act (21 U.S.C. 352(f)(1); 21 CFR 201.5, 201.100(c)(2)). Moreover, falsely labeling a biological product is prohibited under section 351(b) of the PHS Act without regard to any interstate commerce nexus (42 U.S.C. 262(b)). The act contains a presumption of interstate commerce for devices (section 709 of the act (21 U.S.C. 379a)).

Both the PHS Act and the act provide authority for enforcement of the various statutory requirements. FDA is authorized to conduct inspections to determine compliance with regulatory requirements (42 U.S.C. 262(c) and 21

U.S.C. 360(h) and 374). Approved PMA's may be suspended or revoked (42 U.S.C. 262(a) and 21 U.S.C. 355(e) and 360e(e)). Biological products and devices may be recalled under certain circumstances (42 U.S.C. 262(d)(2) and 21 U.S.C. 360h). Judicial actions, including seizures, injunctions, and criminal prosecutions, may also be initiated (42 U.S.C. 262(f) and 21 U.S.C. 332, 333, and 334).

Some products may contain a combination of biological products and drugs or devices. Under a provision of the Safe Medical Devices Act of 1990, FDA determines the primary mode of action of the combination products (21 U.S.C. 353(g)), then assigns the primary jurisdiction for review of the product within the agency based on that determination. FDA has established procedures for designating the organization within FDA (i.e., the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), or the Center for Devices and Radiological Health (CDRH)) to review combination products or any other products where the agency center with primary jurisdiction is unclear (21 CFR 3.1 through 3.10). CBER, CDER, and CDRH have also entered into intercenter agreements to clarify the centers' responsibilities for reviewing various kinds of products.

B. Regulation of Somatic Cell and Gene Therapy Products

This statement is intended to present the agency's current approach to regulating somatic cell and gene therapy products. For the purpose of this statement, somatic cell therapy products are defined as autologous (i.e., self), allogeneic (i.e., intra-species), or xenogeneic (i.e., inter-species) cells that have been propagated, expanded, selected, pharmacologically treated, or otherwise altered in biological characteristics *ex vivo* to be administered to humans and applicable to the prevention, treatment, cure, diagnosis, or mitigation of disease or injuries. Cellular products intended for use as somatic cell therapy are biological products subject to regulation pursuant to the PHS Act (42 U.S.C. 262) and also fall within the definition of drugs in the act (21 U.S.C. 321(g)). As biological products, somatic cell therapy products are subject to establishment and product licensure to ensure product safety, purity, and potency. At the investigational stage, these products must be in compliance with part 312. Clinical trials are, therefore, to be conducted under IND's. As drugs, somatic cell therapy products are also

subject to drug requirements such as conformity with CGMP regulations.

FDA has not required premarketing approval for many types of transplantation, including bone marrow transplants. However, recent scientific and biotechnological developments now enable bone marrow to be manufactured into a somatic cell therapy product. Such products are subject to FDA regulation consistent with the approach to other somatic cell therapies described in this statement. In addition, other forms of transplantation, such as the transfer of whole organs and tissues, have been, or are currently being reassessed and addressed by FDA or other Federal agencies in light of current knowledge and technological advances.

Gene therapy products are defined for the purpose of this statement as products containing genetic material administered to modify or manipulate the expression of genetic material or to alter the biological properties of living cells. Some gene therapy products (e.g., those containing viral vectors) to be administered to humans fall within the definition of biological products and are subject to the licensing provisions of the PHS Act, as well as to the drug provisions of the act. Other gene therapy products, such as chemically synthesized products, meet the drug definition but not the biological product definition and are regulated under the relevant provisions of the act only.

Biological products intended for use as source materials for further manufacture into licensed somatic cell therapy products or gene therapy products require premarketing approval as biological products intended for further manufacture when they are shipped from one legal entity to another. Such products would be considered part of a shared manufacturing arrangement in which: (1) Two or more manufacturers perform different aspects of the manufacture of a product, (2) neither performs nor is licensed to perform all aspects of the manufacture, and (3) each manufacturer holds product and establishment license applications. In a shared manufacturing arrangement, FDA accepts only license applications for biological products intended for further manufacture that specify the licensed manufacturer or manufacturers to which the intermediate product will be shipped and approves such applications only after demonstration of safety and efficacy of the end product. For example, biological gene therapy products intended for use *ex vivo* in the manufacture of genetically altered cells for somatic cell therapies will require premarketing approval as biological

products intended for further manufacture when shipped from one legal entity to another and will be approved only when the final somatic cell therapy product is approved. For further discussion regarding shared manufacturing, refer to FDA's policy statement concerning cooperative manufacturing arrangements for licensed biological products, which was published in the *Federal Register* on November 25, 1992 (57 FR 55544).

In accordance with the statutory provisions governing biological products and drugs, a somatic cell therapy product or gene therapy product must be the subject of an IND in compliance with part 312 or of an approved PLA regardless of whether the finished product is shipped across State lines.

The manufacture of somatic cell therapy products or gene therapy products will involve many ancillary products used as part of the manufacturing process. The ancillary products are not intended to be present in final products but may have an impact on the safety, purity, or potency of the products under manufacture. Such ancillary products meet the definition of devices and, if marketed, will be regulated under the act device authorities, with the appropriate type of regulatory control being determined according to codified procedures (e.g., investigational device exemption (IDE)—21 CFR part 812; premarket approval (PMA)—21 CFR part 814; premarket notification (510(k))—21 CFR 870.81 through 807.97). When these ancillary products are used in the manufacturing of somatic cell or gene therapy products, they become subject to drug CGMP's, in particular for components and containers (21 CFR 211.80 through 211.94 and 211.101(b) and (c)).

Some of the ancillary products will already be marketed as medical devices, drugs, or biological products. When an ancillary product used as a component of the manufacturing process is marketed but not labeled for the specific use, such use may initially be described under the IND for the final somatic cell or gene therapy product. Such use of ancillary products by manufacturers of investigational somatic cell therapy or gene therapy products is contingent upon the submission of complete descriptions of the use of the ancillary product in the manufacturing process.

If the ancillary product used as a component of the manufacturing process does not have marketing approval, manufacturers of the somatic cell or gene therapy product must submit or provide cross-reference to a

complete description of the manufacturing process, specifications, qualification, and acceptance criteria of the ancillary product. This information may be filed by the sponsor of the IND for the somatic cell or gene therapy product, may be filed in an IND or IDE by the manufacturer of an ancillary product, or may be made available by the manufacturer of the ancillary product in a master file format, as defined in 21 CFR 814.3(d) and discussed in 21 CFR 814.20(c).

Manufacturers who wish to market ancillary products for use in the manufacturing of somatic cell or gene therapy products must file either: (1) A 510(k), (2) a PMA, (3) an amendment to an existing 510(k), PMA, NDA, or PLA.

The manufacture of somatic cell therapy products or gene therapy products may involve components of manufacture intentionally present as part of the final products. Products containing both a somatic cell component and another drug or device component in the final product will be handled as combination products.

The following statement succinctly describes FDA's current approach to regulating somatic cell therapy and gene therapy products with primary emphasis on premarket approval issues. As previously discussed, products that meet the biologic, drug, or device definition must also comply with other relevant provisions of the PHS Act and the act. Manufacturers may also find useful information in FDA's document entitled "Points to Consider in Human Somatic Cell Therapy and Gene Therapy," Docket No. 91N-0428, available from CBER's Congressional and Consumer Affairs Branch (address above).

III. Statement

A. Somatic Cell Therapy

1. Definition

Somatic cell therapy is the prevention, treatment, cure, diagnosis, or mitigation of disease or injuries in humans by the administration of autologous, allogeneic, or xenogeneic cells that have been manipulated or altered ex vivo. Manufacture of products for somatic cell therapy involves the ex vivo propagation, expansion, selection, or pharmacologic treatment of cells, or other alteration of their biological characteristics.

2. Cells Subject To Licensure as Final Products When Intended for Use as Somatic Cell Therapy

Cells subject to licensure as final biological products when intended for use as somatic cell therapy include cells

manipulated in a way that changes the biological characteristics of the cell population (e.g., by expansion, selection, encapsulation, activation, or genetic modification as a part of gene therapy as defined in section III.B.1. of this document).

Examples include the following: (1) Autologous or allogeneic lymphocytes activated and expanded ex vivo (e.g., lymphokine-activated killer cells (LAK), tumor infiltrating lymphocytes (TIL cells), antigen specific clones); (2) encapsulated autologous, allogeneic, or xenogeneic cells or cultured cell lines intended to secrete a bioactive factor or factors (e.g., insulin, growth hormone, a neurotransmitter); (3) autologous or allogeneic somatic cells (e.g., hepatocytes, myocytes, fibroblasts, bone marrow- or blood-derived hematopoietic stem cells, lymphocytes) that have been genetically modified; (4) cultured cell lines; and (5) autologous or allogeneic bone marrow transplants using expanded or activated bone marrow cells. (For bone marrow products whose status is not clear, consult CBER.)

3. Cells and Tissues Subject to Licensure as Source Material

Cells and tissues subject to biological product licensure as source material include allogeneic or xenogeneic cells harvested by other than the final product license holder and intended for manufacture into a somatic cell product. Examples include the following: (1) Muscle cells removed from donors and shipped to a manufacturer for expansion into a muscle cell therapy, (2) animal cells harvested at an animal care facility and shipped to a manufacturer for encapsulation or other manufacturing steps into a somatic cell therapy, and (3) other human tissue harvested from donors and shipped to another legal entity for manufacture into a somatic cell therapy.

4. Cells for Which Applications for Approval Prior to Marketing are not Presently Required

Cells for which applications for approval prior to marketing are not required at the present time include the following: (1) Cell transplants not having the characteristics described in sections III.A.2. and III.A.3. of this document, and (2) minimally manipulated or purged bone marrow transplants. Examples include the following: (1) Allogeneic bone marrow transplantation employing ex vivo T cell purging with a monoclonal antibody approved for such purging, (2) autologous bone marrow transplantation employing ex vivo tumor cell purging by an approved agent, and (3)

autologous bone marrow transplantation employing bone marrow enriched for stem cells by immunoadherence. (However, extensive manipulation of bone marrow for the purpose of obtaining purified stem cell populations would result in a somatic cell therapy subject to licensure.)

B. Gene Therapy

1. Definition

Gene therapy is a medical intervention based on modification of the genetic material of living cells. Cells may be modified *ex vivo* for subsequent administration or may be altered *in vivo* by gene therapy products given directly to the subject. When the genetic manipulation is performed *ex vivo* on cells that are then administered to the patient, this is also a type of somatic cell therapy. The genetic manipulation may be intended to prevent, treat, cure, diagnose, or mitigate disease or injuries in humans.

2. Final Products Containing the Genetic Material Intended for Gene Therapy

Final products containing the genetic material intended for gene therapy are regulated as biological products requiring PLA's (e.g., viral vectors containing genetic material to be transferred, *ex vivo* transduced cells and analogous products) or as drugs requiring NDA's (e.g., synthetic products) regardless of whether they are intended for use *in vivo* or *ex vivo*. Gene therapy products that are licensed biological products will be approved as biological products intended for further manufacture if they are intended to be used *ex vivo* during the manufacture of genetically altered cells.

Examples include the following: (1) A synthetic polynucleotide sequence intended to alter a specific genetic sequence in human somatic cells after systemic administration is regulated as a drug requiring an NDA; (2) a retroviral vector containing the adenosine deaminase (ADA) gene, intended to be administered intravenously to the patient, is regulated as a biological product requiring a PLA; and (3) a

retroviral vector containing the ADA gene and intended to modify cells *ex vivo* is regulated as a biological product intended for further manufacture requiring a PLA.

3. Viral Vector Systems Intended for Further Manufacture Into Final Products

The manufacture and quality control of viral vector systems (i.e., not containing the complete genetic material) that are designed to serve as the starting point for further manufacture into final products (i.e., insertion of additional genetic material into the vector) may be described in a drug master file.

C. Ancillary Products Used during Production of Somatic Cell Therapies

Numerous products will be used during production of somatic cell therapy. Examples include the following: (1) Bioreactors and cell culturing systems, (2) components of culture media, (3) drug- or biologic-like components used to activate or otherwise change the biological characteristics of the cells, (4) certain antisense polynucleotides, and (5) agents used to purge or select or stimulate specific cell populations. A common characteristic of these products is that they are intended to act on the cells, rather than to have an independent effect on the patient. Additionally, the intended action of these products is not dependent upon incorporation into the somatic cell with maintenance of the products' structural or functional integrity.

These products meet the definition of medical devices. They are regulated as devices, with the type of regulatory control being determined according to codified procedures. In contrast, products administered directly to patients or products whose function requires incorporation into the somatic cells with maintenance to some degree of structural or functional integrity (e.g., viral or other vectors containing genetic material to be used in gene therapy) are not considered ancillary products; rather, they are regulated as drugs or biological products.

The center primarily responsible for regulating a particular device will be designated according to the current intercenter agreements. For example, according to the current agreement, CDER will regulate the synthetic antisense compounds, CBER will be responsible for monoclonal antibody-based purging agents, and CDRH will oversee the approval of bioreactors.

D. Combination Products

Many somatic cell products administered to patients will be combinations of a biological product and a device or of a drug, a biological product, and a device. Examples include the following: (1) Encapsulated pancreatic islet cells secreting insulin, and (2) a device containing encapsulated cells secreting a neurotransmitter. The combination products for which the primary mechanism of action is that of the somatic cell therapy component will be regulated as biological products.

IV. Comments

FDA recognizes that somatic cell and gene therapy products constitute a new and emerging scientific area. The agency will review and consider written comments on the regulatory approach set forth in this notice. Any comments received will be considered in determining whether amendments to, or revisions of, the approach are warranted. Two copies of any comments should be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments received are available for public examination in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

Dated: September 24, 1993.

Michael R. Taylor,

Deputy Commissioner for Policy.

[FR Doc. 93-24938 Filed 10-13-93; 8:45 am]

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