[DOCKET NO.]

DRAFT

DRAFT DOCUMENT CONCERNING THE REGULATION OF PERIPHERAL BLOOD HEMATOPOIETIC STEM CELL PRODUCTS INTENDED FOR TRANSPLANTATION OR FURTHER MANUFACTURE INTO INJECTABLE PRODUCTS

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DRAFT DOCUMENT CONCERNING THE REGULATION OF PERIPHERAL BLOOD HEMATOPOIETIC STEM CELL PRODUCTS INTENDED FOR TRANSPLANTATION OR FURTHER MANUFACTURE INTO INJECTABLE PRODUCTS

PURPOSE

The purpose of this document is to set forth the approach that Food and Drug Administration (FDA) believes is appropriate for the regulation of peripheral blood hematopoietic stem cell products (hereafter referred to as peripheral blood stem cell products) intended for transplantation or as source material for further manufacture into injectable products. Prior to fully implementing this approach, FDA is providing individuals with an opportunity to comment on this draft document. FDA will publish in the Federal Register a Notice of Availability of this document, asking that comments be provided to the Dockets Management Branch (address provided on the cover page), by close of business on [insert date].

I. INTRODUCTION

The field of hematologic transplantation has changed substantially during the last two decades. Improved understanding of the diverse aspects of human hematologic precursors has facilitated their experimental manipulation. Our knowledge of their localization in humans during both fetal and postnatal development, growth regulation, differentiation, homing, and phenotypic and functional characteristics has facilitated the development of new methods of transplantation. Traditional bone marrow transplantation, involving extraction of bone marrow by aspiration from bone cavities and processing by density centrifugation, is increasingly being supplanted by novel approaches that include use of peripheral blood cells and procedures to purify and expand hematopoietic stem cells. Human peripheral blood, which can be enriched in hematopoietic stem cells by a variety of interventions, has emerged as an alternative source of

hematopoietic cells for bone marrow reconstitution.

FDA has not required premarketing approval for many types of transplantation, including bone marrow transplantation. Federal oversight currently exists in two areas related to human bone marrow transplantation. First, development of standards for unrelated donor marrow transplants as mandated in the Transplant Amendments Act of 1990 was originally assigned to the National Institutes of Health (NIH) and now is handled by the Health Resources and Services Administration. Second, extensive manipulation of human blood, bone marrow or other sources, for the purpose of obtaining enriched stem cell populations, renders them a somatic cell therapy product subject to licensure by the FDA. (For further information regarding somatic cell therapies, see "Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products; Notice", F.R. Vol. 58, No. 197, October 14, 1993.)

Recently, the Agency has reviewed a number of applications for investigational new drugs (INDs), as well as investigational device exemptions (IDEs) and pre-market device applications including Premarket Approval Applications (PMAs) and premarket notifications (510(k)s), in which hematopoietic stem cells for transplantation were derived from peripheral blood. Existing FDA statutory authorities apply to these new products and allow FDA to assess whether such areas as quality control, quality assurance, safety, purity, potency and efficacy are appropriately assessed prior to marketing. This draft document outlines the current regulatory approach that FDA believes is appropriate for the regulation of stem cells derived from peripheral blood.

II. BACKGROUND

A. Legal Authorities

FDA regulates numerous products intended to prevent, treat, or diagnose diseases or injuries of man 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 "drugs", 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 (21 U.S.C. 321(h)), in part, as "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article(s) … 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." The definitions of both "drug" and "device" also include articles "intended to affect the structure or any function of the body."

Section 351(a) of the PHS Act requires that biological products be manufactured at facilities holding active licenses. Licenses are 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 are subject to the requirements of 21 CFR part 312. FDA's regulations for MOST biological products currently specify the submission of both a product license application (PLA) (21 CFR 601.20) and an establishment license application (ELA) (21 CFR 601.1 through 601.10). Biologics establishments and products must meet the standards set forth in the regulations (21 CFR parts 600 through 680).

Section 351(b) of the PHS Act prohibits falsely labeling or marketing 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, 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)). The drug and device CGMP regulations are codified at 21 CFR parts 211 and 820.

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 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, 610 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, 607, and 807.

The interstate commerce nexus needed to require premarket approval under the statutory provisions governing biologics, drugs, and devices 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 other applicable premarket approval) 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 interstate commerce (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. 379(a)).

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 and 21 U.S.C. 360h and 374). Approved PLAs may be suspended or revoked (42 U.S.C. 262) and approval of NDAs and PMAs may be withdrawn (21 U.S.C. 355(e) and 360e). An order to recall biological products or devices may be issued 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).

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) for that same product.

Some products may contain a combination of biological products, drugs and/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 Peripheral Blood Stem Cells

This draft document is intended to present the approach that the FDA believes is appropriate for regulating human peripheral blood stem cells. For the purpose of this document, peripheral blood stem cell products are defined as hematopoietic cells derived from peripheral blood to be administered to humans and applicable to the prevention, treatment, cure, diagnosis, or mitigation of disease or injuries in humans. FDA believes that the safety, potency, and purity of these products is best assured at this time by regulating these products as biologics pursuant to the PHS Act (42 U.S.C. 262) and that these products fall within the definition of drugs and are subject to the laws promulgated in the Act (21 U.S.C. 321(g)). As biologicals, peripheral blood stem cell products are subject to establishment and product licensure to ensure product safety, purity, and potency (21 CFR, parts 600, 601, 610, and 640) and are subject to establishment registration and product listing (21 CFR, part 607) as well as to requirements of Current Good Manufacturing Practice (CGMP) regulations (21 CFR 211, 606).

1. Peripheral Blood Stem Cells intended for transplantation.

The peripheral blood stem cells are by nature blood and blood components. In many cases, this material may be collected by establishments that also collect blood or other components for transfusion. These facilities operate under existing industry standards and CGMPs for Finished Pharmaceuticals (21 CFR part 211), CGMPs for Blood and Blood Components (21 CFR part 606), the General Biologic Product Standards (21 CFR parts 600 and 610), and the Additional Standards for Human Blood and Blood Products (21 CFR part 640). For blood and blood components intended for transfusion and shipped in interstate commerce, both the establishment and the product are required to be licensed. These same provisions apply to peripheral blood stem cell products intended for transplantation. FDA believes that the blood and blood component model as described above is the appropriate regulatory approach for non-manipulated PBSCs for transplantation. However, FDA believes that manipulated PBSCs should be evaluated for safety and efficacy under IND and be subject to licensure.

2. Peripheral Blood Stem Cells as Source Materials for Further Manufacture.

> **FDA requests that potential manufacturers of gene therapy products comment on the impact of the sections which apply to peripheral blood stem cells used as source material for further manufacture. Those sections are entitled Peripheral Blood Stem Cells as Source Materials for Further Manufacture and Non-manipulated Peripheral Blood Stem Cells Subject to Licensure as Source Materials.**

Peripheral blood stem cell products intended for use as source materials for further manufacture into licensed biological products should also be licensed as biological products intended for further manufacture, unless regulated under the license of the final product. If different from

cells that are licensed by conformance to accepted PBSC standards, source materials may be subject to an IND. Because the agency recognizes that blood cells intended for further manufacture may be provided by suppliers other than traditional blood establishments, such products could, for example, be considered part of a cooperative manufacturing arrangement in which: (1) two or more manufacturers perform different aspects of the manufacture of a product that ordinarily would warrant separate licensing, (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 may accept for filing 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, human peripheral blood intended for use in the manufacture of stem cell products for hematopoietic support/reconstitution would be licensed as a blood product intended for further manufacture when shipped from one legal entity to another. In such a shared manufacturing situation, FDA would license the biological product intended for further manufacture only after determining that the final product is safe and effective. Autologous cells shipped in interstate commerce for use in the further manufacture of some autologous products (for example, gene therapy products) may be evaluated as part of the manufacturing of the final product. For further information regarding cooperative 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).

3. Ancillary products for production of peripheral blood stem cells.

The manufacture of peripheral blood stem cell products may involve the use of ancillary products in the manufacturing process. These are not part of the final stem cell product and are

intended to act solely on the cells and not have an independent effect on the patient. The use of ancillary products may have an impact on the safety, purity, or potency of the final products. When these ancillary products are used in the manufacturing of hematopoietic stem cell products, they are subject to either drug or device CGMP's, as applicable.

Ancillary products which are not already regulated under an existing IND, IDE, NDA, PLA, PMA, or 510(k) meet the definition of devices and, if marketed, may be regulated under the medical device authorities of the Act, 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 807.81 through 807.97). Manufacturers who wish to market ancillary products separately for use in the manufacturing of hematopoietic stem cell products should file either: (1) a 510(k), (2) a PMA, or (3) an amendment to an existing 510(k), PMA, NDA, or PLA, depending on the type of ancillary product. Ancillary products which are approved devices, may be subject to a different regulatory mechanism if a manufacturer seeks the addition of an indication where the product is intended to have a direct effect on the patient.

If the ancillary product used as a component in the manufacturing process is not the subject of an approved premarketing application, the manufacturers of the hematopoietic stem cell product should submit or cross-reference a description of the manufacturing process, specifications, qualification, and acceptance criteria of the ancillary product in their application. This information may be filed by the sponsor of the IND for the hematopoietic stem cell 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).

Some ancillary products used in the manufacture of PBSCs 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 is not labeled for the specific use, such use may initially

be described under the IND for the final hematopoietic stem cell product. Such use of ancillary products by manufacturers of investigational hematopoietic stem cell products is contingent upon the submission of complete descriptions of the use of the ancillary product in the manufacturing process.

The manufacture of hematopoietic stem cell products may involve the addition of other components intentionally present as part of the final products. Final products containing both a hematopoietic stem cell component and another drug or device component in the final product will be handled as combination products.

The following draft statement describes the approach FDA believes is appropriate for regulating peripheral blood stem cell products. 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.

III. DRAFT STATEMENT OF PROPOSED REGULATORY APPROACH

A. Peripheral Blood Stem Cell Products

1. Definition

Peripheral blood stem cell products are defined as products containing hematopoietic progenitor cells derived from peripheral blood to be administered to humans and applicable to the prevention, treatment, cure, diagnosis, or mitigation of disease or injuries.

These products can be considered in two groups based on the degree of manipulation necessary to obtain the final product or other considerations.

a. "Manipulated peripheral blood stem cells" are defined as 1) products obtained after one or more procedures have been performed to intentionally purge or enrich the starting material of a subset(s) of nucleated cells or 2) a product subject to licensure as a somatic cell therapy as defined in the Federal Register published on October 14, 1993 (58 FR 53248). It should be noted that the present definition of "manipulated peripheral blood stem cell product" includes some products addressed in the FDA Application of Current Statutory Authorities to Human Somatic Cell Therapy and Gene Therapy Products document (58 FR 53248) and the additional products described in III.A.1.a. above. Examples of procedures that result in manipulated products include centrifugal elutriation, negative or positive cell selection by monoclonal antibody-based technologies, cell populations expanded in vitro using cytokines or other procedures leading to a somatic cell therapy product.

b. Non-manipulated or minimally manipulated peripheral blood stem cells (hereafter referred to as non-manipulated cells) are defined as products that have not been subjected to a procedure(s) that selectively removes, enriches, expands or functionally alters specific nucleated cell populations. Procedures performed ex vivo include: centrifugation and density gradient separation, lysis of contaminating erythrocytes, addition of medium for cryopreservation, transfer of product from collection devices to storage containers, and storage in liquid or frozen state. The removal of polymorphonuclear leukocytes also would not be considered manipulation. Non-manipulated peripheral blood stem cells may include stem cells mobilized in vivo by biological or drug products approved for such use.

2. Manipulated Peripheral Blood Stem Cell Products Subject to Licensure as Final Products When Intended for Transplantation

Manipulated peripheral blood stem cells intended for use in the prevention, treatment, cure, diagnosis, or mitigation of disease or injuries in humans are subject to IND regulations

during clinical development and, as final biological products are subject to licensure. Examples include but are not limited to: 1) peripheral blood-derived mononuclear cells enriched for CD34+ cells; 2) peripheral blood-derived mononuclear cells depleted of tumor cells; and 3) peripheral blood-derived mononuclear cells depleted of T lymphocytes using devices or products such as monoclonal antibodies and complement for hematopoietic reconstitution.

3. Non-manipulated Peripheral Blood Stem Cells Subject to CGMPs, Blood Establishment Registration, and licensure.

When intended for use in the prevention, treatment, cure, diagnosis, or mitigation of disease or injuries in humans, FDA does not expect the submission of IND applications to evaluate safety and efficacy for hematopoietic stem cells that are isolated from peripheral blood without manipulation (III.A.1.b.). However, if these products are intended for distribution in interstate commerce, licensure of the product and establishment is required.

FDA requires manufacturers of these products to register as blood establishments (21 CFR 607). They must operate according to applicable blood CGMPs and are subject to FDA inspection. Non-manipulated peripheral blood stem cells can be licensed when they meet the product specifications and standards for collection, processing, and storage. These standards are presently under development by the FDA. Because of the probable introduction into interstate commerce, manufacturers of products intended for use in allogeneic transplantation should obtain product and establishment licenses.

4. Non-manipulated Peripheral Blood Stem Cells Subject to Licensure as Source Materials

Non-manipulated peripheral blood stem cells intended as a source material for further manufacture into a final hematopoietic stem cell product are also subject to licensure unless

regulated under the license for the final product. Often, source material is manufactured by other than the final product license holder and shipped from one legal entity to another. Products to be utilized as source materials can only be approved when the final product (such as the genetically altered cell) is approved. Examples include peripheral blood stem cells intended for ex vivo expansion or as targets of gene transfer and expression. Evaluation of source material which is manufactured differently from accepted standards, may be subject to IND regulation.

B. Ancillary Products Used During Production of Peripheral Blood Stem Cell Products

Numerous products will be used during the production of peripheral blood stem cell products. A common characteristic of many 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 peripheral blood stem cell product with maintenance of the structural or functional integrity of the ancillary product is maintained. These products meet the definition of medical devices. They may be regulated as devices, with the type of regulatory control determined according to codified procedures. Examples include, but are not limited to: 1) apheresis machines; 2) equipment for purging or selecting stem cell populations; 3) growth factors used for in vitro stimulation or expansion; and 4) collection and storage containers.

In contrast to products described above, products administered directly to patients or products whose function requires incorporation into the hematopoietic stem cell product with maintenance to some degree of structural or functional integrity are not considered medical devices; rather, they are regulated as drugs or biological products. Examples include, but are not limited to: 1) investigational agents administered to stem cell donors to mobilize the stem cell populations before collection of the product, e.g., unlicensed cytokines or cytokines not licensed for this indication; 2) anticoagulants added to the collection container and infused with the product into the recipient; and 3) storage medium

and cryoprotective agents added to the stored product and infused with the product into the recipient.

IV. COMMENTS

Peripheral blood stem cell products used for hematologic transplantation constitute a new and emerging scientific area. The Agency will review and consider written comments on the regulatory approach set forth in this notice. 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.