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DRAFT

DRAFT DOCUMENT CONCERNING THE REGULATION OF PLACENTAL/UMBILICAL CORD BLOOD STEM CELL PRODUCTS INTENDED FOR TRANSPLANTATION OR FURTHER MANUFACTURE INTO INJECTABLE PRODUCTS

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DRAFT DOCUMENT CONCERNING THE REGULATION OF PLACENTAL/UMBILICAL CORD BLOOD STEM CELL PRODUCTS INTENDED FOR TRANSPLANTATION OR FURTHER MANUFACTURE INTO INJECTABLE PRODUCTS

PURPOSE

The purpose of this document is to set forth the regulatory approach that the Food and Drug Administration (FDA) believes is appropriate for the regulation of placental/umbilical cord blood stem cell products (hereinafter referred to as cord blood stem cell products) intended for transplantation or further manufacturing into injectable products. Prior to fully implementing this approach, FDA is providing individuals with an opportunity to comment on this draft document. FDA is asking that comments be provided to the Agency during the comment period provided in the Notice of Availability, published in the FEDERAL REGISTER on February 26, 1996, to Dockets Management Branch (address provided on the cover page). In the interim, individuals wishing to pursue clinical investigations involving these products may submit investigational new drug applications (INDs) to the Division of Blood Applications, Center for Biologics Evaluation and Research (CBER), FDA.

I. INTRODUCTION

Traditional bone marrow transplantation, involving the extraction of bone marrow by aspiration from bone cavities and processing by density gradient centrifugation, is increasingly being supplanted by novel sources of stem cells and biotechnologic procedures to purify and expand hematopoietic stem cells. Human cord blood, which is enriched with pluripotent hematopoietic stem cells, has recently emerged as an alternative source of hematopoietic stem cells for patients who are unable to obtain stem cells from allogeneic donors. Cord blood stem cells have potential therapeutic value for hematopoietic reconstitution in malignant and genetic diseases. Although availability of cord blood stem cells may reduce some constraints on bone marrow transplantation, the ultimate safety and efficacy of cord blood stem cell transplantation has yet to be determined.

Recently, the Agency has received numerous inquiries regarding its regulatory approach to cord blood stem cell products. Cord blood stem cells for transplantation in autologous or allogeneic recipients is an emerging area with complex medical issues, including issues raised by the banking of such cells

for possible future transplantation. Unlike bone marrow donors who usually have several years of medical history, cord blood is obtained from a newborn donor without an established medical history. Existing FDA statutory authorities apply to these new products and allow the FDA to assess whether areas such as quality control and quality assurance, safety, purity, potency, and efficacy are appropriately addressed prior to marketing. This draft statement outlines the regulatory approach that FDA believes is appropriate for the regulation of cord blood stem cell products.

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 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 regulations for biological products currently specify the submission of both product license applications (PLAs) (21 CFR 601.20) and establishment license applications (ELAs) (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. Therefore, 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 the manufacture, processing, packing and holding or installation conform with current good manufacturing practices (CGMPs) 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 with the frequency suggested in the labelling (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 in 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 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. 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(c) and 21 U.S.C. 360(h) and 374). Approved PLAs may be suspended or revoked (42 U.S.C. 262) and approval of new drug applications (NDAs) and device premarket approval applications (PMAs) may be withdrawn (21 U.S.C.

355(e) and 360e(e)). 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 applicable 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 an NDA or PMA.

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., 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 Human Cord Blood Stem Cells

This document is intended to present the approach that the FDA believes is appropriate for regulating human cord blood stem cells. For the purpose of this document, cord blood stem cell products are defined as autologous (i.e., self) or allogeneic (i.e., intra-species) products which contain hematopoietic stem cells derived from placental/umbilical cord blood and which are to be administered to humans and are applicable to the prevention, treatment, cure, diagnosis, or mitigation of disease or injuries. FDA believes that the safety, potency and purity of these products can only be assured at this time by regulating these products as biologics, pursuant to the PHS Act (42 USC 262) and, that these products fall within the definition of drugs and are subject to the regulations promulgated under the FDC Act (21 USC 321(g)). As biological

products, cord blood stem cell products are subject to product licensure to ensure product safety, purity and potency (21 CFR parts 211 and 610) and are subject to establishment licensure (21 CFR part 601). Establishments collecting cord blood stem cells should consider the concepts found in blood regulations (21 CFR parts 606 and 640) and relevant FDA recommendations to blood establishments. Many of these concepts may be included in licensing requirements.

Cord Blood Stem Cells as source materials for further manufacture.

Cord blood stem cells intended for use as source material for further manufacture into licensed hematopoietic stem cell products should also be licensed as a biological product, unless regulated under the license of the final product. The agency recognizes that cord blood stem cells intended for further manufacture could 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 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, human cord blood intended for use in the manufacture of stem cell products for hematopoietic support/reconstitution should be licensed as a blood product for further manufacture and will be approved when the final product is approved. 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).

Ancillary products for production of cord blood stem cells.

The manufacture of cord blood stem cell products may involve ancillary products used as part of the manufacturing process. These products are not intended to be present in final products but may have an impact on the safety, purity, or

potency of the products. Ancillary products which are not already regulated under an existing IND, NDA, PLA, PMA, or premarket notification (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), PMA, (21 CFR part 814), 510(k), (21 CFR 807.81 through 807.97)). When ancillary products are used in the manufacturing of cord blood stem cell products, their use becomes subject to either drug or device CGMP's, as applicable. 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. 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 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.

If the ancillary product used as a component of the manufacturing process does not have pre-marketing approval, manufacturers of the hematopoietic stem cell product should submit or cross-reference 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 hematopoietic stem cell product, may be filed in an IND or IDE by the manufacturer of an ancillary product, as appropriate, 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).

The manufacture of cord blood stem cell products may involve components of manufacture intentionally present as part of the final products. Products containing both a cord blood 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 that FDA believes is appropriate for regulating cord 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 act and the PHS Act.

III. DRAFT STATEMENT

A. Cord Blood Stem Cell Products

1. Definition

Cord blood stem cell products are defined as products containing hematopoietic progenitor cells derived from placental/umbilical cord blood to be administered to humans and applicable to the prevention, treatment, cure, diagnosis, or mitigation of disease or injuries. Cord blood may be subjected to a variety of processing procedures to obtain a final product. The extent of manipulation of cord blood cells should not affect the regulatory mechanism for pre-market approval. FDA notes that one or more procedures can be performed to intentionally purge or enrich the starting material of a

subset(s) of nucleated cells, other than polymorphonuclear leukocytes, can result in the manufacturing of a manipulated cord blood stem cell product. Examples of procedures that result in manipulated products include centrifugal elutriation, negative or positive cell selection by monoclonal antibody-based technologies, cytokine expanded cell populations and other procedures leading to a somatic cell therapy product (58 FR 53247, October 14, 1993).

Cord blood stem cell products may also be obtained from minimally manipulated cord blood that has not been subjected to a procedure(s) that selectively removes, enriches, expands or functionally alters specific nucleated cell populations (other than polymorphonuclear leukocytes). Procedures that are considered to be minimal manipulation 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.

2. Cord Blood Stem Cell Products Subject to Licensure

as Final Products When Intended for Use in Humans

When intended for use in the prevention, treatment, cure, diagnosis, or mitigation of disease or injuries in humans, cord blood stem cell products, regardless of the extent of manipulation, are subject to IND regulations during clinical development and, as final biological products are subject to licensure.

3. Cord Blood Stem Cells Subject to Licensure as Source Materials

Cord 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 of the final product. This 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 will be approved only when the final product (such as a genetically altered cell) is approved.

B. Ancillary Products Used During Production of Cord

Blood Stem Cell Products

Numerous products may be used during the production of cord blood stem cell products. 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 hematopoietic stem cell product with maintenance of the product's structural or functional integrity. 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; and 3) collection and storage containers.

In contrast to products described above, products administered directly to patients or products whose function requires incorporation into the cord blood 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) anticoagulants added to the collection container and infused with the product into the recipient; and 2) storage medium and cryoprotective agents added to the stored product and infused with the product into the recipient.

IV. COMMENTS

Cord 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 draft regulatory approach set forth in this document 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.