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Docket Number 97N-484P
Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No: 97N-484P; Current Good Tissue Practices for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement

Dear Sir or Madam:

This letter comments on the above-referenced proposed rule. As background, we first provide an introduction section on the regulatory framework for human cellular and tissue-based products. Next, we request that FDA: (1) revise the proposed "distribution" definition, (2) clarify the "significant step" definition, (3) revise the "availability for distribution" requirement, (4) minimize the tracking requirements, and (5) clarify examples of acceptable homologous use labeling claims.

I. Introduction

Based on its authority under section 361 of the Public Health Service Act ("PHSA"), FDA has published three proposed rules and one final rule on the regulation of human cellular and tissue-based products (HCT/Ps). On May 14, 1998, FDA published the first rule, which requires manufacturers of certain HCT/Ps to register with the agency and list their products. Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products, 63 Fed. Reg. 26744 (May 14, 1998) (hereinafter referred to as "proposed registration rule"). FDA finalized this rule on January 19, 2001. Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing, 66 Fed. Reg. 5447 (Jan. 19, 2001) (hereinafter referred to as "final registration rule").

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On September 30, 1999, FDA published the second proposed rule, which would require certain manufacturers of HCT/Ps to screen and test the donors of cells and tissue used in these products for risk factors and for clinical evidence of communicable diseases. Suitability Determination for Donors of Human Cellular and Tissue-Based Products, 64 Fed. Reg. 52696 (Sept. 30, 1999) (hereinafter referred to as "proposed suitability rule").

On January 8, 2001, FDA published this rule, the Current Good Tissue Practice for Manufacturers of Tissue-Based Products, which proposes, among other things, regulations that would govern the manufacture and distribution of HCTPs. Current Good Tissue Practices for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement 66 Fed. Reg. 1508, 1551 (Jan. 8, 2001) (hereinafter referred to as "proposed cGTP rule"). This proposed rule completes FDA's set of proposals for regulating HCTPs and attempts to "improve protection of the public health while permitting significant innovation and keeping regulatory burden to a minimum." Id. at 1508.

While many of the proposed requirements in the cGTP proposal are reasonable, a number of the requirements in the proposed rule should be revised, clarified, or removed in order to allow for significant innovation in the manufacture of HCT/Ps and minimize the regulatory burden on entities involved in the manufacture of HCT/Ps.

II. Revise "Distribution" Definition To Exclude Entities That Do NOT Take Possession of HCT/Ps

There is a glaring inconsistency in the definition of "distribution" contained in the proposed cGTP rule and the final registration rule. There should be only one definition of "distribution" for part 1271, and it should exclude entities involved in distribution that do NOT take possession of HCT/P's. FDA should, therefore, modify the proposed definition of "distribution" in the proposed cGTP rule to be consistent with the distribution definition in the final registration rule.

> Under the proposed cGTP rule, distribution is defined as:
> any conveyance or shipment of human cellular or tissue-based products (including importation and exportation), whether or not such conveyance or shipment is entirely intrastate and whether or not possession of the product is taken.

66 Fed. Reg. 1508, 1551 (Jan. 8, 2001) (1271.3(jj)) (emphasis added).

In marked contrast, the final registration rule clearly excludes entities that do not take possession of HCT/P's from the distribution definition --- "distribute" means "the conveyance or shipment of an HCT/P . . . and an entity that does not take possession of HCT/Ps is not distributing them for the purposes of this rule." See 66 Fed. Reg. at 5456. This distinction makes sense because an entity that does not physically possess HCT/Ps should not be required to register, list, or comply with cGTPs since it is not actually handling HCT/Ps.

The proposed cGTP distribution definition, however, ostensibly applies to any entity that is involved in the conveyance or shipment of HCT/Ps, even though that entity may not take physical possession of HCT/Ps. For example, entities that merely took orders for HCT/Ps, but did not handle product, would be distributors under the proposed rule.

This broad definition of distribution does not comport with the actual goals of the proposed rule. The proposed rule is designed to ensure that "cells and tissues are handled properly . . . to prevent contamination and to preserve tissue function and integrity." 66 Fed. Reg. 1508, 1508 (Jan. 8, 2001). There is no valid health-based reason to require entities that do not take possession of HCT/Ps to comply with cGTPs. As proposed, this definition would lead to the ludicrous result of requiring entities to establish and follow GTPs for the manufacture of product, even though those entities do not take possession of HCT/Ps.

FDA should, therefore, remove the "whether or not possession is taken" language from the cGTP distribution definition, and clearly state that entities that do not take possession of HCT/Ps are not distributors within the meaning of the cGTP rule. Otherwise, it is completely illogical (not to mention confusing) to have an entity be considered a distributor under one of the HCT/P rules, and not a distributor under another HCT/P rule. Accordingly, FDA should revise the distribution definition in the proposed cGTP rule to clarify that only entities that take possession of HCT/Ps are distributors.

III. Clarify What Constitutes a "Significant Step"

Proposed section 1271.180 would require entities that perform "significant steps" in the manufacture of HCT/Ps to "establish and maintain" procedures for those significant steps to ensure the function and integrity of the product. See 66 Fed. Reg. at 1514, 1553. This requirement is confusing.

First, there is no definition of "significant steps" that would assist an entity in determining whether its procedures were considered significant. The one example of a

significant step in the proposal, "recovery of cells or tissue" is fairly obvious. More examples of what does and does not constitute a significant step are needed. Second, the procedure requirement does not seem to differ from the proposed "quality program" requirement, which requires "an establishment that performs any step in the manufacture of [HCT/Ps to] establish and maintain a quality program" that functions to ensure that appropriate procedures are established and maintained. 66 Fed. Reg. 1552 (proposed § 1271.160)). Additional clarification on the significant step/procedure proposal is requested.

IV. Remove "Availability for Distribution" Requirement From Receipt & Distribution Section

Generally, section 1271.265 details the proposed requirements for the receipt and distribution of HCT/P products. For the most part, this section appears to apply to the activities of the actual distributor of HCT/Ps--i.e., receiving and shipping of already released and packaged HCT/Ps, etc.-- as opposed to activities involving the actual manufacture or processing of HCT/Ps.

Section 1271.265(c), however, establishes procedures and requirements for "availability [of HCT/Ps] for distribution," which, among other things, provides that:

> procedures shall be established and maintained for making [HCT/Ps] available for distribution. These procedures, which shall include release criteria, shall be designed to prevent the release of products that are in quarantine, are contaminated, have deteriorated, or otherwise have been manufactured in violation of current good tissue practices, . . . Prior to making a [HCT/P] available for distribution, the establishment shall verify and document that the release criteria have been met, and review all records pertaining to the product.

Id. at 1556.

As the definition states, "available for distribution" means "that the [HCT/P] has been determined to meet all release specifications and to be suitable for distribution." Id. at 1551. (1271.3(f)(f))

The "availability for distribution" requirement should only apply to entities that actually provide the finished HCT/Ps to distributors (i.e., the processors/manufacturers of HCT/P), not to the actual distributors themselves. The reason that this requirement is so important is that the proposed rule has assigned ultimate and overall responsibility for the product to the establishment that is responsible for making the product available for

distribution. Id. at 1512. The entity that determines that a product meets release criteria and therefore makes the product available for distribution, whether or not that entity is the actual distributor, is the entity responsible for ensuring the compliance with the requirements of the cGTP rule. Id. at 1512, 1552 (proposed 1271.150(2)). This is a significant regulatory burden, and should appropriately fall only on the entity that is responsible for providing the finished and packaged HCT/P to the distributor, consignee, hospital or doctor.

As drafted in this part of the rule, however, it is unclear what entity will be responsible for this "availability for distribution" requirement. As drafted, it appears that this requirement is being placed on entities that have no involvement in the manufacture of the product, but merely deliver and distribute product that has already been released for distribution by another entity. The "availability for distribution" determination should be made only by the entity that processes the product, verifies that release criteria have been met, and then provides the HCT/P for distribution.

FDA should, therefore, remove this requirement from the receipt and distribution part of the rule, and move it to the parts that deal with the manufacturing controls and processing for tissue--i.e., 1271.220, .225, .230. In the alternative, FDA should clearly state that the "availability for distribution" requirement set forth in proposed 1271.265(c), only applies to entities that provide the HCT/Ps to distributors for distribution, and it does NOT apply to distributors themselves.

V. Minimize Tracking Requirements

FDA should minimize the tracking requirements because the current proposal is overly broad and burdensome. While it makes sense to require tracking of HCT/Ps both from donor to recipient or final disposition and from final disposition or recipient to donor, this requirement should not burden every entity that is involved with the distribution of HCT/Ps.

FDA is on the right track by allowing "establishments that perform some, but not all, of the steps in the manufacturing process to participate in a method of product tracking that has been established by another establishment responsible for other steps in the manufacture process." Id. at 1519. This should be expanded so all establishments further down in the production line, other than the establishments that screen the HCT/Ps or process and manufacture HCT/Ps, merely follow the already existing tracking procedures set up by other entities. Otherwise, it will be cumbersome to have four different types of tracking procedures executed by four different types of entities involved in the manufacture of HCT/P. FDA should, therefore, expand on this proposal by clearly placing the tracking responsibility on the entity that makes the product

available for distribution, and allowing subsequent entities in the production chain (i.e., distributors) to follow that entities existing tracking procedures.

VI. Clarify Acceptable Homologous Labeling Claims

The preamble to Section 1271.370(b)(2) explains that:

> a labeling claim or promotional materials regarding the therapeutic or clinical outcome of a human cellular or tissue based product (other than for reconstruction, replacement, repair, or supplementation of cells or tissue) would be considered a claim for a use other than a nonhomologous use.

Id. at 1521 (emphasis added).

If a HCT/P product is labeled in a nonhomolgous manner, then the product and the labeling "shall be regulated under section 351 of the PHS Act and/or the Federal Food, Drug and Cosmetic Act." Id. at 1558 (1271.370(b)(2)).

In the final registration rule, FDA acknowledged that "the use of bone for repair, replacement or reconstruction anywhere in the skeleton of the recipient (including the vertebral column) would be considered homologous use." 66 Fed. Reg. 5447, 5458 (Jan. 18, 2001).

Piecing these two rules together, it appears that materials regarding the therapeutic or clinical outcome of bone used in spinal surgery would be considered a claim for a homologous use. Therefore, a manufacturer of HCT/Ps could promote the results of a clinical trial on HCT/Ps used for spinal fusion, or reveal the results of an x-ray of a HCT/P used in reconstructive spine or other orthopedic surgery, and still be promoting the HCT/P for a homologous use. FDA should clarify this rule to identify examples of homologous use claims (such as those identified above).

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In sum, FDA should revise the distribution definition to exclude entities that do not take possession of HCT/Ps, clarify the meaning of "significant steps," remove the "availability for distribution" requirement from the receipt and distribution section, minimize tracking requirements, and acknowledge in the final rule that labeling or promotional claims regarding the use of bone in orthopedic surgeries are considered homologous use claims.

Respectfully submitted,

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