

KING & SPALDING

1730 PENNSYLVANIA AVENUE, N.W.
WASHINGTON, D.C. 20006-4706
TELEPHONE: 202/737-0500
FACSIMILE: 202/626-3737

DIRECT DIAL:

EMB: 202-626-2903
AW: 202-626-5615

ebasile@kslaw.com
awhitesides@kslaw.com

3748 '99 DEC 28 PM 2:05

December 28, 1999

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

RE: Proposed Rule: Donor Suitability Determination for Donors of Human Cellular and Tissue-Based Products

Dear Dockets Management Branch:

This letter comments on the proposed rule published on September 30, 1999 in the Federal Register, "Suitability Determination for Donors of Human Cellular and Tissue-Based Products" 64 Fed. Reg. 52696 (hereinafter referred to as "proposed suitability rule").

I. Background

The proposed suitability rule requires manufacturers of human cellular and tissue-based products to screen and test the donors of cells and tissues used in those products for communicable disease agents and diseases. The proposed suitability rule is the second in a series of rules proposed by FDA, which reflects FDA's proposed comprehensive system of regulation for human cellular and tissue-based products. The first of these human cellular and tissue-based rules, proposed on May 14, 1999 in the Federal Register, "Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products," 63 Fed. Reg. 26744 (hereinafter referred to as "proposed registration rule"), is referred to and amended by the proposed suitability rule.

The proposed suitability rule amends the criteria set forth in the proposed registration rule. The criteria establishes whether a human cellular or tissue-based product will be regulated tissue product under section 361 of the Public Health Service Act (so-called "361 products"),

97N 484S

C227

191 PEACHTREE STREET
ATLANTA, GA 30303-1763
TELEPHONE: 404/572-4600
FACSIMILE: 404/572-5100

1185 AVENUE OF THE AMERICAS
NEW YORK, NY 10036-4003
TELEPHONE: 212/556-2100
FACSIMILE: 212/556-2222

1100 LOUISIANA STREET, SUITE 3300
HOUSTON, TX 77002-5219
TELEPHONE: 713/751-3200
FACSIMILE: 713/751-3290

or as a medical device under the Federal Food, Drug and Cosmetic Act ("FFDCA"). A product will be regulated as tissue, and not as a device so long as it:

- 1) Is minimally manipulated;
- 2) Is not promoted or labeled for any use other than a homologous use;
- 3) Is not combined with or modified by the addition of any component that is a drug or a device; and
- 4) Either does not have a systemic effect, or has a systemic effect and is for autologous use, family related allogeneic use or reproductive use.

64 Fed. Reg. at 52720 (to be codified at 21 C.F.R. § 1271.10).

There are significant problems with FDA's approach to regulating human cellular and tissue-based products. First, as a procedural matter, FDA fails to follow the Administrative Procedure Act ("APA") by relying on a legal framework that has not been finalized through notice and comment rulemaking pursuant to 5 U.S.C. § 553. Second, from a substantive perspective, FDA's criteria for determining whether a tissue product is regulated as a medical device or as tissue is vague and overbroad and could result in excessive and unnecessary regulation of numerous tissue products as devices.

II. FDA Must Finalize Proposed Regulations

FDA's rulemaking scheme does not comport with administrative law requirements. FDA proposed the registration rule in May of 1998, and did not finalize the rule before it proposed the suitability rule. FDA's proposed suitability rule refers to, and relies on, definitions and proposed regulations in the proposed registration rule, although these definitions and requirements are not final. In order for agency regulations to be valid and binding, FDA must follow the procedures set forth in § 553 of the APA, and must: 1) provide public notice of the proposed rule, 2) receive and consider comments on the proposed rule, 3) issue a final rule that meaningfully responds to public comments and states the basis and purpose of the rule. 5 U.S.C. § 553(b) & (c).

By layering proposed rule upon proposed rule, FDA is creating a morass of intertwining proposed regulations that do not have the binding effect of law, yet purport to establish further regulation of tissue by relying on the previous unfinalized regulations. This building block regulatory approach does not allow the public to adequately comment on proposals in the individual rules and violates the APA. In addition, FDA's approach contradicts its previous pronouncement with regard to tissue regulation, when it stated that it "plans to finalize [requirements set forth in 21 C.F.R. pt 1270] and then engage in further rule making as necessary." Proposed Approach to Regulation of Cellular and Tissue-Based Products at 14 n.5 (Feb. 28, 1997).

To afford the public meaningful participation with respect to the proposed rules, FDA must consider alternatives presented in public comments before it incorporates the proposed rule in proposed regulation after regulation.

It is a tenant of administrative law that “ an agency is required to provide opportunity for comments, which means that the agency’s mind must be open to considering them.” Grand Canyon Air Tour Coalition v. FAA, 154 F.3d 455, 456 (D.C. Cir. 1998). By using definitions and requirements set forth in the unfinalized registration rule in the proposed suitability rule, FDA demonstrates that it is not only failing to consider and respond to public comments that suggest alternatives to the registration rule, but that it has invalidly determined that the rule is the final pronouncement of agency policy.

Even more problematic is that while the proposed suitability rule references the proposed registration rule, it at the same time amends certain definitions in the proposed registration rule. See e.g., 64 Fed. Reg. at 52699 (“FDA is now making several modifications to proposed §§ 1271.1, 1271.10, and 1271.20 as they appeared in the proposed registration rule”). FDA should not amend the proposed registration rule in the proposed suitability rule. Instead, FDA should re-propose the registration rule so that the public can adequately comment on the definitions initially proposed in the registration rule.

The definitions in the proposed regulations are key to determining the scope and impact of the proposed rules. Without a formal and final pronouncement of the criteria, it is very difficult to gauge the impact of the regulations on industry and consumers, which in turn makes it difficult for the public to adequately comment on the substance of the proposed regulation.

III. FDA’s Tissue Criteria Are Unclear

The “homologous use” and “minimally manipulated” criteria for determining whether a human cellular and tissue-based product is subject to regulation as a medical device or tissue must be removed because these criteria do not adequately define most tissue-based products that are currently regulated as tissue as “tissue.” See Proposed Section 1271. 10 (“Criteria for Regulation of Human Cellular and Tissue-Based Products Solely Under § 361 of the PHS Act”).

Currently, homologous use is defined to mean:

[T]he use of a cellular or tissue-based product for replacement or supplementation and:

1) for structural tissue-based products, occurs when the tissue is used for the same basic function that it fulfills in its native state, in a location where such structural function normally occurs; or

2) for cellular and nonstructural tissue-based products, occurs when the cells or tissue is used to perform the function(s) that they perform in the donor.

64 Fed Reg. at 52700 (to be codified at § 1271.3(d)).

The homologous use definition does not adequately define most tissue products that are regulated currently as tissue. For example, the “fulfills in its native state, in a location where such structural function normally occurs” language is unclear and too narrow: it implies that in order for the product to be regulated as tissue, it must be used in the identical place and for identical purposes from which the tissue was removed. This ignores the realistic use of most tissue products that are now regulated as tissue, and that should be regulated as tissue, but are nevertheless used in a way that may be somewhat different than its function or use in the native state.

With regard to homologous promotion or labeling, FDA proposes that tissue products are those that are not promoted or labeled for any use other than a homologous one. 64 Fed Reg. 52696, 52720. While FDA should remove the homologous criteria altogether from the proposed rule, if the homologous criteria remains, FDA should also retain the requirement that the homologous determination should be based solely on promotion and labeling.

The minimally manipulated criterion does not adequately define tissue products that should be regulated as tissue. In the proposed suitability and registration rules, minimal manipulation is defined to mean:

- 1) for structural tissue, processing that does not alter the original relevant characteristics of the tissue relating to the tissue’s utility for reconstruction, repair, or replacement; and
- 2) for cells or nonstructural tissues, processing that does not alter the relevant biological characteristics of cells or tissues.

Id. (to be codified at § 1271.3(g)).

It is impossible to draw a meaningful distinction between tissue products that are “minimally manipulated” and those that are “more than minimally manipulated.” Due to the difficulty of determining how much manipulation is acceptable in order for the product to be regulated as tissue, any tissue product that has been manipulated in any fashion could be considered “more than minimally manipulated.” This will lead to confusion over the distinction between tissue products regulated as tissue and tissue products regulated as devices, and will lead to more products being regulated as devices than are necessary.

Accordingly, FDA should remove the minimally manipulated criteria. Instead, we propose that the tissue versus device definition should be whether the tissue product is labeled for tissue replacement, reconstruction or restoration of function. We would propose that the new criteria define tissue products, which would be regulated as tissue, as products that are "not promoted or labeled for any use other than tissue replacement, reconstruction or restoration of function."

If labeled for replacement, reconstruction or restoration of function, the amount of manipulation of the tissue should not be a factor. For example, the medical community routinely manipulates bone tissue into a variety of shapes and sizes. These practices will continue regardless of the amount of regulation FDA imposes. It is in the patient's best interest that these manipulations be performed by tissue banks, under controlled circumstances and according to precise specifications, rather than by surgeons in the operating room. As currently proposed, all FDA's regulation will do is shift the manipulation from the tissue bank to the surgeon in the operating room. Surely, this cannot be what FDA intends.

* * * * *

FDA should finalize the proposed registration rule prior to issuing new regulations and in doing so, should eliminate the minimal manipulation and homologous use criteria for defining tissue products. The proposed homologous use and minimally manipulation criteria do not accurately capture the differences between tissue products that are, and should be, regulated as tissue. Instead of the minimal manipulation criterion, FDA should propose that tissue products that are labeled or promoted for tissue replacement, reconstruction or restoration of function be regulated as tissue.

Sincerely,



Edward M. Basile



Ashley Whitesides