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October 27, 2000

BY HAND DELIVERY

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: FDA Docket No. 00N-1380; Human Bone Allograft: Manipulation and Homologous Use in Spine and Other Orthopedic Reconstruction and Repair

Dear Sir or Madam:

The following comments are adapted from my presentation at the August 2, 2000 public meeting on behalf of Regeneration Technologies, Inc. The objective of that presentation was to comment on legal issues raised by the Food and Drug Administration's (FDA's) proposed regulatory framework for human tissue-based products from the perspective of bone allograft processors, and to suggest approaches that the agency could take to address those issues.

I. The Proposed "Minimal Manipulation" and "Homologous Use" Risk-Factor Criteria Are Excessively Vague

As several speakers commented during the meeting, and as noted in a significant portion of the written comments submitted to FDA on the "Establishment Registration and

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Listing for Manufacturers of Human Cellular and Tissue-Based Products”¹ and “Suitability Determination for Donors of Human Cellular and Tissue-Based Products”² proposed rules, the “minimal manipulation” and “homologous use” risk-factor criteria, which FDA proposes to use in determining how stringently tissue-based products will be regulated, are vague and open-ended. This vagueness gives rise to at least two legal issues: one concerning the adequacy of the public notice afforded by FDA’s proposed rules, and the other concerning whether the present definitions of the proposed criteria, if finalized, would be adequate to afford regulated persons constitutional due process.

A. Inadequate Notice Under the Administrative Procedures Act (APA)

To participate meaningfully in the notice-and-comment rulemaking process required by the APA, interested parties must have fair notice of the basis and meaning of an agency’s proposal. 5 U.S.C. § 553(b). See also, e.g., American Medical Ass’n v. Reno, 57 F.3d 1129, 1132 (D.C. Cir. 1995) (“Notice of a proposed rule must include sufficient detail on its content and basis in law and evidence to allow for meaningful and informed comment”); Home Box Office, Inc. v. FCC, 567 F.2d 9, 55 (D.C. Cir.) (a proposed rule must contain sufficient information to allow informed “adversarial critique”), cert. denied, 434 U.S. 829 (1977). FDA’s proposed “minimal manipulation” and “homologous use” criteria, both key components of the agency’s proposed approach, fall short of this requirement. Compare McLouth Steel Prods. Corp. v. Thomas, 838 F.2d 1317, 1323 (D.C. Cir. 1988) (notice inadequate for failure to provide explanation of systematic approach for calculating probable contamination levels); American Iron & Steel Inst. v. EPA, 568 F.2d 284, 291 (3d Cir. 1977) (notice inadequate for failure to indicate manufacturing processes

¹ 63 Fed. Reg. 26744 (May 14, 1998) (FDA Docket No. 97N-484R).

² 64 Fed. Reg. 52696 (Sept. 30, 1999) (FDA Docket No. 97N-484S).

covered by proposed regulations); Wagner Elec. Corp. v. Volpe, 466 F.2d 1013, 1019-20 (3d Cir. 1972) (notice inadequate because only certain manufacturers would grasp link between the subject identified and the broader subject of the final rule). Questions posed by some of the meeting attendees following the presentations given by FDA officials are illustrative of this point.

For example, one tissue industry representative stated with respect to the "homologous use" criterion:

I have a question about the word "location" in the homologous use definition. As you know, most traditional bone allograft products are used in recipients in other locations from where they are taken at the time of donation. I wonder if you could elaborate a little bit on when you say "location," whether you mean direct, one-for-one use of a donor tissue in an analogous site in a recipient.

Transcript (Tr.) at 40. Another meeting attendee expressed uncertainty regarding whether bone used for fusion would fit under the definition:

[I]f you look at the fusion referred to earlier, where putting bone where a disc is, that is the intended purpose. You are not trying to replace a disk, you are trying to fuse two bony segments. So, that is the intended purpose, that always has been the purpose. You are not trying to replace a disc with a bone. So in that sense, you have a question of is that the same function, the same location.

Id. at 44. A third attendee commented:

I am still confused with the definition. One of the common uses for cancellous bone is not for bone repair, but for fusion of wrists, ankles, knee disorders, and so on. Also, cancellous bone is often used for cortical disruption. So, I am still not sure on how we are applying that definition to these applications.

Id. at 45. Each of these comments illustrates the lack of clarity in the proposal.

According to FDA's proposal, meeting or not meeting the proposed "minimal manipulation" and "homologous use" criteria will in most cases mean the difference between premarket approval requirements and no premarket approval requirements for a product. This is a significant regulatory consequence in that the Federal Food, Drug, and Cosmetic Act (FDC Act) prohibits commercial distribution of articles that do not possess the required FDA marketing approval. See, e.g., 21 U.S.C. §§ 331(a), 331(d), 351(f), 355(a). Commercial distribution of articles in violation of the FDC Act is subject to civil and criminal penalties. Id. § 333. Thus, lack of clarity in the final rule will place companies in peril of regulatory enforcement actions.

Only with additional specificity and examples can tissue processors and other interested parties be expected to comprehend how the proposed "minimal manipulation" and "homologous use" criteria will affect particular products, and thereby submit meaningful comments. Thus, if FDA intends to promulgate the criteria as final regulations, it should re-propose them with more specificity and examples of the kinds of processing and uses *that the agency believes these terms to encompass*. One FDA official at the meeting proffered that the agency had provided adequate examples in its 1997 "A Proposed Approach to the Regulation of Cellular and Tissue-Based Products" document, and in its two proposed rules. Tr. at 225.³ However, the written comments submitted to the agency,

³ Another FDA official reported that it "seemed . . . a lot of the comments . . . were based on misinformation which was spread by certain interested parties . . . that these regulations would regulate all bone allografts as devices . . ." Id. at 33. Although FDA's proposed rules did not explicitly state that all bone allografts used in the spine will be regulated as devices, that appeared to have been FDA's conclusion. After FDA cancelled the panel meeting to classify bone dowels as devices, interested parties obtained and reviewed the briefing materials provided to

the speaker presentations at the meeting, and the questions posed by meeting attendees, all demonstrate otherwise.

B. Constitutional Vagueness

Constitutional due process requires that federal laws and regulations provide regulated persons with fair notice and a reasonable degree of certainty as to what is required for compliance. See, e.g., Grayned v. City of Rockford, 408 U.S. 104, 108 (1972); Freeman United Coal Mining Co. v. Federal Mine Safety and Health Review Comm'n, 108 F.3d 358, 362 (D.C. Cir. 1997) ("In order to satisfy constitutional due process requirements, regulations must be sufficiently specific to give regulated parties adequate notice of the conduct they require or prohibit"); General Elec. Co. v. EPA, 53 F.3d 1324, 1333-34 (D.C. Cir. 1995) ("Where . . . regulations . . . are unclear, . . . and where the agency itself struggles to provide a definitive reading of the regulatory requirements, a regulated party is not 'on notice' of the agency's ultimate interpretation of the regulations, and may not be punished"). Federal laws and regulations must also provide clear standards to regulators to prevent arbitrary and subjective enforcement. See, e.g., Kolender v. Lawson, 461 U.S. 352, 357 (1983); Grayned, 408 U.S. at 108.

panel members. The materials revealed that the agency had already decided bone dowels were devices; the only remaining question was whether they should be Class II or Class III. FDA's position was that dowels were not homologous since they were intended to fuse the areas between vertebrae where the agency believed bone did not normally occur. However, as several speakers noted during the public meeting, the vast majority of bone allografts used in the spine are used for fusion. If FDA considered fusion of vertebrae with a bone dowel to be non-homologous, rendering the bone dowel a device, then presumably, the agency would consider all bone allograft used to fuse the spine (or other areas of the body that are normally not fused) to be non-homologous, and therefore devices, under the proposed framework.

As currently formulated, the proposed “minimal manipulation” and “homologous use” criteria give FDA virtually unlimited discretion to decide on an ad hoc basis what falls within and outside of these categories.

FDA’s ostensible solution to the vagueness problem, offered in its proposals, is to recommend that tissue processors consult the agency with respect to products for which they are uncertain how the criteria apply. This case-by-case, “consult-the-agency” approach does not redress the constitutional infirmities. Moreover, this approach is not practical unless the criteria and FDA’s procedures for interpreting and applying the criteria are reasonably clear to begin with. If they are not, then tissue processors will be compelled to seek an opinion on virtually every product they plan to develop and distribute.

The potential for this undesirable result is exemplified by FDA’s recent effort to classify bone dowels as devices. Prior to announcing the classification panel meeting, FDA stated in the 1998 proposed establishment registration and listing rule that “minimal manipulation” included the very methods that are used to process bone dowels – e.g., “cutting, grinding, and shaping, soaking in antibiotic solution; sterilization by ethylene oxide treatment or irradiation; . . . lyophilization . . . ; and freezing.” 63 Fed. Reg. at 26748. FDA also stated that “homologous use” included “bone allograft obtained from a long bone but labeled for use in a vertebra. . . .” *Id.* at 26749. Based on these statements, processors of bone dowels reasonably concluded that FDA considered bone dowels to be minimally manipulated and homologous, and therefore subject to regulation as tissue. Until FDA announced the panel meeting to classify bone dowels, it would not have occurred to most processors that there was even any need to consult the agency regarding their regulatory status. In addition, submitting inquiries to FDA and waiting for an answer based on unclear criteria will not cure the proposal’s constitutional flaws.

II. The Tissue Reference Group

Another issue raised by FDA's proposed framework concerns the role and authority of the Tissue Reference Group (TRG), and the procedures employed by that group to perform its appointed functions.

The TRG is only briefly mentioned in FDA's "Proposed Approach" document. Strangely, the group and its functions are not discussed or even mentioned in the 1998 establishment registration and listing or 1999 donor suitability proposed rules.⁴ According to the TRG's "Manual of Standard Operating Procedures and Policies," this intra-agency group was established to serve as a "single reference point" for "product specific questions" concerning "jurisdiction, policy, and regulations." The TRG's 1998 Annual Report states, among other things, that the TRG has authority to make recommendations regarding a whole class of products. To date, the TRG has issued at least 12 recommendations regarding how new tissue-based products will be regulated.

It appears from the limited descriptions of the TRG recommendations that FDA has made available, that they were dependent at least in part on the group's interpretation and application of the proposed risk-based criteria (e.g., "minimal manipulation" and "homologous use") to specific products.⁵ Making jurisdictional recommendations based on the risk-based criteria is a rather significant responsibility with important regulatory

⁴ This is another aspect of the rulemaking proceeding for which the agency appears not to have given adequate notice.

⁵ Indeed, during the public meeting, an FDA official stated that although "[w]e would never just make a recommendation based on things that we have not yet finalized," "[w]hen we arrive at our decisions, the decision is based on how the product would fit under the definition currently in effect under the final rule, as well as how it might be viewed under the proposed approach." Tr. at 225, 224 (emphasis added).

consequences for it not to be described for public consideration and comment in FDA's rulemaking proceeding.⁶ The Request for Designation regulations in 21 C.F.R. Part 3 were promulgated through notice-and-comment rulemaking. Even they do not authorize the Ombudsman to make jurisdictional determinations with respect to the classifications of entire groups of products.

Another issue is the secrecy with which TRG recommendations are made. A number of speakers at the meeting urged that this recommendation process be made more transparent, and that the agency publish more information about the results of its evaluations. Such information would establish useful precedents on which the industry could rely. Moreover, failure to make more information available could result in repetitive review by the TRG of similarly situated products and in uneven decision-making.

More than one FDA official suggested at the meeting that confidentiality restrictions would preclude additional transparency. We recognize that the TRG recommendations process may involve the review of proprietary trade secret and confidential commercial information that cannot be disclosed, and that determinations of what could be disclosed would have to be made on a case-by-case basis. However, we submit that the benefit of making precedents publicly available is critical to reaching fair, uniform results. Moreover, the need for additional transparency is not limited to the TRG's conclusions regarding individual products and processing methods, but to the internal procedures by which the TRG reviews information and arrives at its recommendations. For example, who actually performs the review? Is review limited to the members of the TRG or does the TRG request input from other agency officials or even outside parties based on their expertise?

⁶ We understand that the device classification panel meeting for bone dowels was the direct result of a TRG recommendation.

Does one member of the TRG conduct a primary review and then present his or her opinion to the rest of the group? Are recommendations made by unanimous consent? By majority vote? What role do the proposed risk-based criteria play? These aspects of the TRG review process would not involve disclosure of confidential information.

Other questions relate to the legal status of the TRG's recommendations and responses to product jurisdiction questions. Presumably, the recommendations would not have the same status as a response to a Request for Designation. Are they more in the nature of "non-binding" guidance? Will they operate to bind the agency in the same manner as an advisory opinion? What, exactly, is their legal status?

FDA should address these issues in its rulemaking proceeding and give interested parties a chance to provide input.

III. "More Than Minimal Manipulation" and "Non-Homologous Use" Should Not Automatically Trigger The Requirement For Premarket Review

An additional issue concerns whether the agency's determination of "more-than-minimal-manipulation" and/or "non-homologous use" with regard to a particular bone allograft is an adequate basis on which to require premarket review. FDA has stated that the purpose of the proposed risk-based criteria is to address factors bearing on the safety and efficacy of tissue-based products. A product's risk is perceived to be greater if the product is more-than-minimally-manipulated and/or promoted for non-homologous use.

As the written comments submitted to FDA and the presentations at the public meeting demonstrate, there is a long history of safe and effective use of bone allografts in the spine to restore stability and function to the spinal column. This history is documented in the medical literature, and by surgeons who use these allografts on a regular basis.

As several speakers noted during the meeting, numerous types of bone allografts have been used safely and successfully in the spine for decades – long before the enactment of the 1976 Medical Device Amendments which first conferred authority on FDA to require premarket review of medical devices. For more than twenty years after this legislation was enacted, the agency made no attempt to regulate most of these allografts as devices. We are not aware of any major new public health threat that would justify an agency move to regulate these allografts as devices now. FDA has already promulgated regulations to address disease transmission concerns (21 C.F.R. Part 1270), and those regulations appear to be working quite well.

Furthermore, organizations such as the Tissue Engineered Medical Product Standards (TEMPS) Group of the American Society of Testing Materials are currently drafting standards that will deal with aspects other than disease transmission about which the agency posed questions during the meeting. In fact, FDA officials are currently involved with the TEMPS working groups that are developing these standards. The agency should not take premature action with respect to bone allografts that could disrupt or undermine the purpose of these standard-making initiatives.

In addition, FDA has suggested with respect to the “minimal manipulation” criterion that it is a moving target in the sense that processing which may at first be considered “more-than-minimal manipulation” may later come to be viewed as “minimal manipulation” based on experience and understanding of the technique. This could result in an uneven playing field for similar products which penalizes innovation by requiring premarket review, while permitting later products less burdensome market entry.

Even if FDA were to determine under its current proposed definitions that certain bone allografts used in the spine are “more-than-minimally manipulated” or “non-homologous,” this does not necessarily mean that premarket review is necessary to ensure

their safety and efficacy. A stated goal of FDA's proposed regulatory approach is to avoid unnecessary and overly burdensome regulation. See, e.g., 63 Fed. Reg. at 26745 ("FDA seeks to achieve several goals with its new approach Primary among them is the improved protection of the public health without the imposition of unnecessary restrictions on research, development, or the availability of new products") (emphasis added). To require premarket review of allografts which already have been shown by the medical literature and the experience of surgeons and recipients to be safe and effective would be contrary to this goal. For example, when FDA attempted to require premarket submissions for heart valve allografts, the continued availability of these allografts was threatened. The agency eventually stipulated in a lawsuit brought by the processors that it would not require premarket submissions. Although today, heart valve allografts are still regulated as devices, the agency has proposed to regulate them as tissue without any requirement for premarket review. 63 Fed. Reg. at 26747. If the agency requires premarket review for bone allografts, their continued availability may be threatened when processors who lack the resources to prepare and submit marketing applications simply stop distributing.

IV. Conclusion and Recommendations

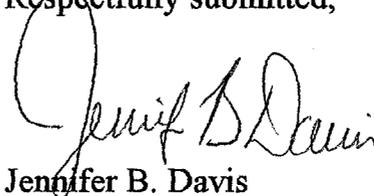
FDA's proposed framework raises significant legal issues concerning, among other things, the authority and function of the TRG, and the definitions, interpretation and application of the proposed risk-based criteria – particularly, "minimal manipulation" and "homologous use."

With regard to how FDA could achieve more clarity in the "minimal manipulation" and "homologous use" criteria, we believe FDA should re-propose the definitions with more specificity and examples of the types of processing and uses *that FDA believes these terms to encompass* and allow the public meaningful opportunity to comment. Another possibility would be to convene a series of "workshops" during which the agency, the

public, processors and users of tissue-based products could participate in a more focused, interactive dialogue.

As for the TRG's significant role in determining how various types of tissue-based products will be regulated, the agency should describe this group's role, authority, functions, processes, and the recommendations process, as well as address the public availability of the TRG's recommendations, in its proposed rulemaking. FDA should also endeavor to make more information about the TRG's recommendations available to the public to minimize repetitive review of similarly situated products, and promote consistent regulatory treatment.

Respectfully submitted,

A handwritten signature in cursive script that reads "Jennifer B. Davis". The signature is written in dark ink and is positioned above the printed name.

Jennifer B. Davis