The American Association of Tissue Banks (AATB) welcomes the opportunity to comment on FDA's final guidance document addressing Validation of Procedures for Processing of Human Tissues Intended for Transplantation, the notice of availability for which was published in the Federal Register on March 13, 2002.1

I. Background

AATB was formed in 1976 to support the development of tissue banking in the United States. By educating its members and developing standards, and through other means, AATB works to help ensure that human tissues intended for transplantation are free of infectious disease and otherwise safe, are of uniform high quality and are supplied in quantities sufficient to meet national needs. The Association's membership currently includes about 1,200 individual professionals and 74 accredited tissue banks engaged in the recovery, processing, storage, and distribution of human tissue. Most of the major tissue banks have obtained AATB accreditation; AATB member banks provide most of the commonly used structural tissues for clinical use.

AATB has consistently supported FDA regulation aimed at assuring the safe and clinically beneficial use of all human tissues provided for transplantation in the U.S. In 1993, AATB publicly supported promulgation of FDA's interim disease transmission regulations for human tissues, which in final form are codified in 21 C.F.R. Part 1270. AATB also supports FDA's donor suitability proposed rule, which is intended to prevent the implantation of tissues obtained from infectious donors, and the provisions of the cGTP proposed rule that are designed to prevent the spread of infectious diseases from contaminated tissues directly to recipients.

FDA has now issued its validation guidance, reminding tissue establishments that Part 1270 requires them to prepare, validate and follow written procedures to prevent infectious disease contamination or cross-contamination during tissue processing. AATB generally supports the guidance. However, we are concerned that one specific aspect of the document exacerbates an ambiguity that began to emerge in FDA policy earlier this year. Specifically, the validation guidance contains a sentence suggesting that tissue establishments may appropriately commingle, or "pool," tissue obtained from different donors during processing. AATB believes this sentence could be interpreted by tissue establishments as tacit FDA approval of pooling, which presents a risk of infectious disease transmission to tissue recipients.

II. The Guidance Calls Into Question FDA's Policy On "Pooling"

Pooling presents a significant risk that agents that are not susceptible to available validated decontamination procedures will be transmitted from tissue to tissue to recipient. As the Director of FDA's Center for Biologics Evaluation and Research (CBER) recognized in congressional testimony last year: "[T]he risks associated with pooling tissues from multiple donors . . . include exposure and possible cross-contamination from one tissue to another tissue of such infectious disease agents as viruses (enveloped and non-enveloped), bacteria, fungi, and prions, including known and emerging infectious agents." The validation guidance itself recognizes that pooling "may increase [the] risk of TSE" and also

acknowledges that there is currently “no adequate validation method for procedures intended to address contamination with TSE-associated prions.”

Since 1989, AATB’s accreditation standards have disapproved the pooling of cells and/or tissue from multiple donors during retrieval, processing, preservation and storage. See AATB, Standards for Tissue Banking § E1.200 (2001). All AATB-accredited establishments are charged with assuring compliance with all applicable accreditation standards. Failure to comply with standards designed to prevent infectious disease contamination and cross-contamination constitutes a material violation of AATB Standards and can result in the withdrawal of or failure to renew a tissue establishment’s AATB accreditation. Over the past decade more than 5 million tissue allografts have been safely transplanted. Relatively few incidents of disease transmission have been reported.

AATB believes that its Standards are consistent with current FDA policy. In 2001, FDA issued its proposed cGTP regulations. Proposed Section 1271.220(c) of the cGTP proposed rule prohibits the pooling of tissues from multiple donors during processing. This proposed prohibition is reiterated in the accompanying preamble. Under FDA’s administrative regulations, a preamble statement represents the agency’s formal position on a subject unless and until formally revoked.

More recent FDA statements, however, have created confusion within the tissue community concerning the permissibility under existing agency policy of pooling or commingling tissue from multiple donors during processing. A January 25, 2002 letter from CBER announces the conclusion of FDA’s compliance review of that firm’s “sterilization” process for allograft tissue. Although the letter states only that regulatory action is not warranted with respect to the process for preventing contamination with conventional infectious agents, AATB is concerned that the letter could be interpreted as authorizing tissue establishments to pool human tissue from multiple donors, provided they also

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6 Proposed 21 C.F.R. § 1271.220(c); 66 Fed. Reg. at 1,516.

7 21 C.F.R. § 10.85(c)(1) & (e). Unlike statutory or regulatory provisions, advisory opinions are not binding on private parties. They do, however, “illustrate acceptable and unacceptable procedures and standards . . .” Id. § 10.85(j). Accordingly, FDA has the authority to make a public statement describing the disease transmission risks of pooling and discouraging tissue establishments from engaging in the practice, even if the agency could not enforce Proposed Section 1271.220(c) by initiating enforcement action against a party who engaged in pooling.
use the “sterilization” process referenced in the letter. The Association has thus requested that FDA clarify its policy on pooling.\(^8\)

FDA’s validation guidance does not address, much less resolve, the ambiguity created by the January 25 letter. Most of the document simply restates the responsibilities of tissue establishments to comply with the validation requirements of 21 C.F.R. Part 1270. The final sentence of footnote 1 of the document states, however: “Commingling of tissue is not expressly prohibited under current regulation.” The guidance thus suggests that current FDA policy allows tissue establishments to “pool” or commingle tissue obtained from multiple donors during processing.

III. Conclusion

AATB is deeply concerned that footnote 1 in the validation guidance could be interpreted as tacit FDA approval of pooling. The Association further believes that tissue establishments might interpret CBER’s January 25 letter as authorizing pooling during processing provided the “sterilization” procedure described in the letter is used.

AATB requests that FDA (1) promptly issue an unambiguous public statement confirming that pooling or commingling tissue from multiple donors during processing presents an unacceptable risk of contamination and thus should not be used by tissue establishments under any circumstances, (2) explain the import of the January 25 letter, and (3) publish a revised validation guidance reiterating its policy.

FDA should confirm that pooling presents an unacceptably high risk of disease transmission to tissue transplant recipients since fully validated methods for preventing the transmission of unconventional agents such as TSE, or of agents that are not yet identified or have not been completely characterized, are not yet available. Given the importance of the public health issues raised by the

\(^8\) On March 5, 2002, AATB requested that CBER confirm that current agency policy does not allow pooling and that CBER’s January 25, 2002, letter is not intended to revoke the pooling policy set forth in the cGTP proposal. Samuel H. Doppelt, M.D., President and P. Robert Rigney, Jr., J.D., Chief Executive Officer, American Association of Tissue Banks to Kathryn C. Zoon, Ph.D., Director, Center for Biologics Evaluation and Research (March 5, 2002) (Tab A). AATB has not yet received a response to its request.
absence, in the validation guidance and elsewhere, of a clear statement of FDA policy opposing pooling, AATB believes it is critical for the agency to take immediate action.

Sincerely,

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