

Guidance for Industry

Validation of Procedures for Processing of Human Tissues Intended for Transplantation

Final Guidance

This guidance is being distributed for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(3) without seeking prior comment because the agency has determined that prior public participation is not appropriate because of recent reports regarding contamination of human tissue intended for transplantation. FDA invites comments on this document. Please submit comments at anytime to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*. FDA will review any comments we receive and revise the guidance document when appropriate.

Additional copies of this guidance document are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at <http://www.fda.gov/cber/guidelines.htm>.

For questions on the content of the document contact Office of Compliance and Biologics Quality at 301-827-6201.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
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This guidance document represents the agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

This guidance document applies to you, all tissue establishments. We, the Food and Drug Administration (FDA), want to remind you that under current FDA regulations, you must prepare, validate, and follow written procedures to prevent infectious disease contamination or cross-contamination (both subsequently referred to as "contamination") during tissue processing (21 CFR 1270.31(d)). Contamination may be caused by a variety of infectious disease agents including viruses, bacteria, fungi, and transmissible spongiform encephalopathy (TSE)-associated prions. The regulations concerning human tissue intended for transplantation are found in 21 CFR parts 1270 and 1271. Relevant portions of the regulation state that:

- *"Processing means any activity performed on tissue, other than tissue recovery, including preparation, preservation for storage, and/or removal from storage to assure the quality and/or sterility of human tissue. Processing includes steps to inactivate and remove adventitious agents."* 21 CFR 1270.3(p).
- *"There shall be written procedures prepared, validated, and followed for prevention of infectious disease contamination or cross-contamination by tissue during processing."* 21 CFR 1270.31(d).
- *"[A]ny facility may use current standard written procedures such as those in a technical manual prepared by another organization, provided the procedures are consistent with and at least as stringent as the requirements of this part."* 21 CFR 1270.31(e).

II. GUIDANCE ON VALIDATION

As we explained in the preamble to Part 1270, the requirement to validate written procedures for preventing contamination by tissues during processing is intended to "facilitate the timely processing of tissue when necessary (e.g., skin and cornea) while maintaining quarantine and continuing current good practices performed by industry in daily tissue processing." (62 FR 40429, 40437, July 29, 1997). Current good practices performed by the tissue industry include

procedures to prevent or reduce the risk of contamination by adventitious agents, such as viruses, bacteria, fungi, and TSE-associated prions, during processing. The procedures used to prevent contamination during processing may vary, depending on the type of tissue and how it is processed. No matter which procedures are chosen, however, you must prepare, validate, and follow those procedures before you release human tissue for transplantation from quarantine (§§1270.31(c) and (d)). If you adopt and use current standard procedures, such as those in a technical manual of another organization, those procedures must be consistent with and at least as stringent as the requirements of Part 1270 (§1270.31(e)). This means that the current standard written procedures you may use have been previously validated as required under §1270.31(d). You are not required to revalidate current standard written procedures; however, you should verify that the procedures have been fully and properly implemented (see below).

Validation shows that the procedure or process is effective, i.e., that you have established by objective evidence that a process consistently produces a result or product meeting its predetermined specifications. The FDA regulations under Part 1270 do not specify how to perform validation. Validation studies conducted by your establishment or by experts in the field may be acceptable. Additionally, we realize that currently, with existing technology, there is no adequate validation method for procedures intended to address contamination with TSE-associated prions. As technology progresses and validation methods become available, you will be required to prepare, validate, and follow procedures to prevent contamination with TSE-associated prions during tissue processing in accordance with §1270.31(d). Moreover, whenever processing may increase risk of TSE, (e.g., commingling of tissues from different donors during processing)¹, we strongly encourage you to prepare and follow procedures now that are scientifically reliable and effective to reduce the risk of TSE-associated prions transmission. For example, heightened screening and stringent recovery procedures may significantly decrease the risk of receiving tissue contaminated with TSE-associated prions before processing. In addition, TSE clearance studies should be considered.

In general, you may obtain validation data to document the effectiveness of a procedure to prevent contamination in several ways, for example, by:

- Verifying full and proper implementation of a previously validated procedure such as may be found in a technical manual of another organization, or
- Conducting literature searches to demonstrate that the procedures implemented are known to be effective in preventing the infectious disease contamination (e.g., Environmental Protection Agency-approved chemical sterilants for laboratory surfaces), or
- Conducting off-line or on-line challenges with indicator organisms, as appropriate, or evaluating the capacity of the manufacturing process to prevent contamination during processing.

¹ In the proposed rule for Current Good Tissue Practice (GTP), FDA has proposed to prohibit the commingling of human cell and tissue-based products from two or more donors during manufacturing (proposed §1271.220(c), 66 FR 1508, 1555, January 8, 2001). We are reviewing comments on this proposal in consideration of a final GTP rule. Commingling of tissue is not expressly prohibited under current regulation.

You must prepare and follow written procedures to prevent infectious disease contamination during processing (§1270.31(d)). Following a written procedure to prevent infectious disease contamination during processing is a significant step in the performance of the requirements under Part 1270. You are required to maintain records concurrently with the performance of each significant step (§1270.33(a)). Therefore, you must document that you and your establishment follow the written procedures you have prepared to prevent infectious disease contamination (§§ 1270.31(d), 1270.33(a)).

During FDA inspections, we may review your validation data to ensure you are using effective procedures to prevent infectious disease contamination (§1270.41(d)). If you do not have validation data or do not follow your validated procedures to prevent contamination, we will include those findings on a List of Inspectional Observations (Form FDA-483) and discuss them with you. We may also collect copies of records for further FDA evaluation, for example, when the validation data are complex or the procedures do not appear adequate to prevent infectious disease contamination (§1270.41(d)).

We encourage you to evaluate your current validation information to ensure that the data demonstrate that the procedures will reliably prevent infectious disease contamination during processing. In your evaluation, you should consider both whether your procedures are effective and whether your validation is adequate. For example, you should ask questions such as:

- Are decontamination procedures for surfaces and instruments that may contact tissue contaminated with viruses (e.g., hepatitis, human immunodeficiency virus) or other pathogenic organisms (e.g., bacteria, fungi) effective in removing or inactivating adventitious agents, so that tissue is not cross-contaminated?
- Are there repeated instances where test results or adverse reaction reports demonstrate that the final product is contaminated? If there is contamination and the positive test results cannot be demonstrated to be due to equipment malfunction or operator error, your validation effort may not have adequately accounted for process variability.

Our current regulations and guidances concerning human tissue intended for transplantation are available at <http://www.fda.gov/cber/tiss.htm>.