Contains Nonbinding Recommendations

Medical Devices Containing Materials Derived from Animal Sources (Except for *In Vitro* Diagnostic Devices)

Guidance for Industry and Food and Drug Administration Staff

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This document supersedes "Medical Devices Containing Materials Derived from Animal Sources (Except for In Vitro Diagnostic Devices)" issued November 6, 1998.

For questions about this document contact Division of Surgical Devices at (301) 796-6970.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Preface

Public Comment

You may submit electronic comments and suggestions at any time for Agency consideration to https://www.regulations.gov. Submit written comments to the Dockets Management Staff, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852. Identify all comments with the docket number FDA-2013-D-1574. Comments may not be acted upon by the Agency until the document is next revised or updated.

Additional Copies

Additional copies are available from the Internet. You may also send an e-mail request to CDRH-Guidance@fda.hhs.gov to receive a copy of the guidance. Please use the document number 2206 to identify the guidance you are requesting.

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Table of Contents

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This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction

The Food and Drug Administration (FDA) is issuing this guidance to update the policy regarding the use of animal-derived material in medical device manufacturing. The role of animal-derived material in medical devices is well established. However, these materials may carry a risk of transmitting infectious disease when improperly collected, stored, or manufactured. The purpose of this guidance is to provide further clarification and updated information on the use of International Organization for Standardization (ISO) 22442-1 "Medical devices utilizing animal tissues and their derivatives – Part 1: Application of risk management," ISO 22442-2, "Medical devices utilizing animal tissues and their derivatives – Part 2: Controls on sourcing, collection and handling," and ISO 22442-3 "Medical devices utilizing animal tissues and their derivatives – Part 3: Validation of the elimination and/or inactivation of viruses and transmissible spongiform encephalopathy (TSE) agents" to support applications to FDA. This guidance also provides recommendations regarding methods for controlling the sourcing of animal tissues with regard to viral pathogens and evaluating the ability of manufacturing methods to remove such pathogens from the final product. This guidance replaces "Medical Devices Containing Materials Derived from Animal Sources (Except for *In Vitro* Diagnostic Devices)" issued November 6, 1998 ("the 1998 guidance.")

For the current edition of the FDA-recognized standard(s) referenced in this document, see the FDA Recognized Consensus Standards Database.[1]

[1] Available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

Throughout this guidance document, the term "we" refers to FDA staff from CDRH. "You" and "your" refers to the manufacturer.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. Background

This guidance updates the 1998 guidance by addressing aspects of potential risk from the use of animal tissues and now includes recommendations related to viral pathogens and all transmissible spongiform encephalopathies (TSEs). The 1998 guidance addressed ways to reduce the potential for exposure to one specific TSE, bovine spongiform encephalopathy (BSE). This document continues to focus on the control of transmissible disease, and contains recommendations for documenting the source of animal tissue and conducting viral inactivation validation studies. Commercial production of animals as sources of bodily tissues used in medical devices can introduce several kinds of risks. The 1998 document primarily addressed geographical factors in the sourcing of the animal tissue. In addition to geographical factors, this document includes recommendations that recognize the role of appropriate animal husbandry to ensure safe tissue sources.

International Standard ISO 22442 series, "Medical devices utilizing animal tissues and their derivatives – Part 1: Application of risk management," "Part 2: Controls on sourcing, collection and handling," and "Part 3: Validation of the elimination and/or inactivation of viruses and transmissible spongiform encephalopathy (TSE) agents," provides recommendations for selection and handling of animal tissues as well as evaluating the risk of pathogen contamination in medical devices. Used in concert with the ISO 22442 series of standards, this guidance is intended to help you identify the possible risks related to medical device components and/or manufacturing reagents that are sourced from animal tissues.

We also recognize that an ISO standard is a document that undergoes periodic review and is subject to revision. Through the FDA standards recognition process, CDRH provides information regarding the extent of recognition of the ISO 22442 series of standards through Supplementary Information Sheets published on the FDA website.[2] FDA will make updates to this guidance document as appropriate, should future revisions to the ISO 22442 series of standards result in significant changes to the recommendations in this document.

[2] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

III. Scope

The information in this guidance is applicable to all medical devices that contain or are exposed (e.g., through a manufacturing reagent) to animal-derived (e.g., bovine, ovine, porcine, avian) materials with the exception of *in vitro* diagnostic devices and materials generally recognized to be safe based on their method of manufacture (e.g., tallow derivatives as described in Annex C of ISO 22442-1: 2015). This guidance addresses the risks of human pathogens that could contaminate animal material and be present in a medical device. For devices that indirectly contact humans, this guidance considers the risk to patients (e.g., how might indirect contact result in pathogen exposure) and the healthcare provider who may handle device components that do not contact a patient.

This guidance provides: 1) information that FDA believes is important to document the safe and consistent manufacture of medical devices containing animal tissue; 2) information that should be included in a premarket submission for products within the scope of this guidance; 3) recommendations regarding how specific aspects of the Quality System (QS) Regulation[3] should be applied to control and document the safe and consistent manufacture of medical devices containing animal tissue; and 4) additional information on specific approaches for determining the ability of manufacturing methods to eliminate viral contamination in the final product. In general, premarket submissions should include information on the specifics identified below or the methods by which the risks are mitigated. In addition, records at the manufacturing facility should continue to document this information on each lot of product manufactured consistent with the QS Regulation.

FDA has developed this guidance document to assist industry in preparing Premarket Approval (PMA) applications, Humanitarian Device Exemption (HDE) applications, Investigational Device Exemption (IDE) applications, Premarket Notification (510(k)) submissions, and De Novo requests for medical devices that contain device components derived from animal sources and come into direct or indirect contact with the human body. This guidance is not applicable to medical devices that are derived from human tissues because the potential contaminants associated with human donor tissues are considerably different than those that are found in animal tissues.

Should a manufacturer have questions about the applicability of this guidance to their specific product, we recommend consultation with FDA.

[3] 21 CFR part 820

IV. Considerations When Using Animal-Derived Materials

A. Control of Animal Tissue Collection

To ensure the safety of medical devices containing or contacting animal tissue, FDA believes that it is important: 1) to document the sourcing and handling of animal tissues as well as 2) to understand the capabilities of the manufacturing and sterilization processes to eliminate human pathogens. Consequently, FDA recommends that you collect and document the information outlined below for animal tissue-derived materials that are used as either device components (e.g., pericardium, viscera, bone, hyaluronic acid, collagen) or manufacturing reagents (e.g., tissue culture media, enzymes). For devices prepared from animal tissues that have a reduced risk of human pathogen contamination (e.g., crustaceans), FDA recommends that you address the information outlined below if applicable to that particular source material. If determined not to be applicable, FDA recommends providing a scientific explanation (i.e., based on published literature or information from a recognized source (e.g., WHO, CDC, USDA)) that identifies the human pathogens that may be present in the animal species, and how your approach ensures device safety.

Premarket submissions should include information on the items identified below, consistent with ISO 22442-2 and the methods by which the risks are mitigated[4] if applicable. You may document this information in a premarket submission or by reference to other regulatory submissions (e.g., Master File, PMA, 510(k)).

- the animal species;
- the age of the animal at slaughter;
- the specific tissue(s) used (if multiple tissues are used, please identify all such tissues);
- the animals' country of origin and residence (with more specific geographic information when appropriate) when such information is available;
- the status of the herd or collection of organisms (e.g., closed herd/group);
- the methods for actively monitoring the health of the herd and the health of specific animals from which tissues are collected (e.g., vaccinations with live modified viruses that can co-purify in the desired tissue, active surveillance for human pathogens);
- the methods and conditions for transporting animal tissue (e.g., tissue refrigeration and quarantine);
- the United States Department of Agriculture (USDA) status of the abattoir;[5]
- the tests performed (and release criteria) for permitting tissue to be further processed and/or combined with other tissues and device components (e.g., a Certificate of Analysis); and
- Material Safety Data Sheets may be helpful information to include in a regulatory submission, when available, because they provide an overview of the safety and

[4] ISO 22442-1, Medical devices utilizing animal tissues and their derivatives – Part 1: Application of risk management

[5] USDA status is not included in ISO 22442-2, however, will provide additional assurance regarding the safety of the tissue used.

potential toxicities related to that component, including information on any reagents used in the processing of the tissue, to support biocompatibility assessments.

Certification of compliance with USDA Animal and Plant Health Inspection Service (APHIS) importation and/or USDA Food Safety and Inspection Service (FSIS) inspection requirements may be provided in lieu of any aforementioned items provided in these forms.

In addition, the manufacturing facility should document 1) procedures for maintaining records on the above cited items[6] and 2) all information outlined above on each lot of product manufactured (Device History Record).[7] If necessary to ensure the safety of the medical device, this information may be reviewed during inspection.

B. Manufacturing Controls for Animal Tissue Components

FDA also recommends that you collect and document the information listed below for each animal-derived material (and facility) used in device manufacture. Premarket submissions should include information on the items identified below and the methods by which the risks are mitigated[8] if applicable. You may document this information in a premarket submission or by reference to other regulatory submissions (e.g., Master File, PMA, 510(k)). The recommended information is:

- test methods and release criteria permitting animal tissues to be further processed and/or combined with other animal tissue(s) or device components for manufacture;
- quarantine procedures for tissues until they have met/failed release criteria;
- test methods and acceptance criteria for assessing in-process and final product bioburden or sterility; and
- methods for facility decontamination/sterilization so that cross-contamination is avoided.

In addition, the manufacturing facility should document: 1) procedures for maintaining records on the above cited items;[9] 2) all information outlined above on each lot of product manufactured (Device History Record);[10] and 3) information to validate the effectiveness of manufacturing equipment cleaning, decontamination, and sterilization relative to the specific pathogen exposure.[11] If necessary to ensure the safety of the medical device, this information may be reviewed during inspection.

The QS Regulation includes requirements related to the methods used in and the facilities and controls used for designing, manufacturing, packaging, labeling, storing, installing, and

[6] 21 CFR 820.70

[7] 21 CFR 820.184

[8] ISO 22442-1, Medical devices utilizing animal tissues and their derivatives – Part 1: Application of risk management

[9] 21 CFR 820.70

[10] 21 CFR 820.184

[11] 21 CFR 820.75

servicing of medical devices. Purchasing Controls, under 21 CFR 820.50, require final device manufacturers to establish procedures that ensure all purchased or otherwise received products and services conform to specified requirements, including those materials derived from animal sources. The controls applied to manufacturing materials are expected to be appropriate to the manufacturing material, the intended use, and the effect of the manufacturing materials on safety and effectiveness (61 FR 52602, 52624). Further information on the QS Regulation for certain premarket applications can be found in "Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff."[12]

C. Sterilization

Because the issues for validating the sterilization of devices containing animal tissue are sufficiently complex to require a case-by-case assessment, we recommend you review the following FDA-recognized consensus standards:

- ISO 11135, Sterilization of health-care products – Ethylene oxide – Requirements for the development, validation and routine control of a sterilization process for medical devices
- ISO 17665-1, Sterilization of health care products – Moist heat – Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices
- ISO 11137-1, Sterilization of health care products – Radiation – Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices
- ISO 11737-1, Sterilization of medical devices – Microbiological methods – Part 1: Determination of a population of microorganisms on products
- ISO 11737-2, Sterilization of medical devices – Microbiological methods – Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process
- ISO 14160, Sterilization of health care products – Liquid chemical sterilizing agents for single-use medical devices utilizing animal tissues and their derivatives – Requirements for characterization, development, validation and routine control of a sterilization process for medical devices
- ISO 14937, Sterilization of health care products – General requirements for characterization of a sterilizing agent and the development, validation, and routine control of a sterilization process for medical devices

In addition, we recommend you contact the FDA staff responsible for reviewing your specific type of device to discuss your sterilization procedures further, if needed.[13]

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[12] Available at https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070899.pdf

[13] Please refer to FDA's guidance, "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff," available at

When a viral pathogen in an animal tissue is part of the risk to the public health for a medical device, we recommend that you consider the extent to which processing and sterilization can inactivate or remove the virus(es). FDA recommendations for validating viral inactivation methods are described below.

Virus Validation Studies

You should assess the processing methods and sterilization techniques used in product manufacture for their ability to inactivate and remove viruses. Viral inactivation data are usually determined by comparing an estimate of the amount of virus in the unprocessed source material with the magnitude of virus inactivation /clearance provided by manufacturing and sterilization processes. As suggested in ISO 22442 Part 3 (Section 5), a review of the published literature should be performed to estimate the amount of virus in the unprocessed source material and to optimize the design of the viral inactivation/elimination study (e.g., selection of model viruses and processing steps to be evaluated). Such studies are generally performed using a scaled down version of specific production and sterilization steps (e.g., acid extraction of collagen or dry heat sterilization) with appropriate model viruses. The model viruses used in these studies should be selected to reflect the actual viral contaminants that may be present in the source animal tissue (e.g., DNA-based and RNA-based, enveloped and non-enveloped viruses).

The results of your viral inactivation studies should demonstrate that the sum of the $\log_{10}$ reduction in virus from selected processing steps and sterilization process(es) (i.e., the overall virus reduction factor) is sufficient to produce a safe product.[14] For example, a device in which virus has been reduced by at least six logs greater than the virus concentration estimated in the unprocessed source material has historically been considered a safe device. A final report describing these studies should be submitted in your premarket submission. This report should discuss: 1) the animal species and tissue source material in the device as well as the amount of virus(es) that might be present in the source material (as identified by in-house research or published literature); 2) the appropriateness of the model viruses selected; 3) the relevance of the conditions used in the virus inactivation studies to the commercial manufacturing methods; and 4) why these studies demonstrate that the final product will be safe.

ISO 22442-3 and the referenced ICH document[15] provide additional insight into the general design and interpretation of viral clearance studies. ISO 22442-3 also recommends, whenever possible, to determine kinetics of viral inactivation to determine the theoretical time necessary to inactivate the total virus population. While such information can be valuable in specific

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https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176, for more information regarding requesting FDA feedback through the Pre-Submission process.

[14] ISO 22442-1, Medical devices utilizing animal tissues and their derivatives – Part 1: Application of risk management

[15] Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin Q5a(R1), available at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5A_R1/Step4/Q5A_R1__Guideline.pdf

circumstances, FDA has found that measurement of the extent of viral inactivation at a single time point, rather than the multiple time points required for a kinetic study, may provide adequate evidence of viral clearance provided that: 1) the model system conditions evaluating viral inactivation closely resemble the conditions of device manufacture; 2) the model viruses tested accurately reflect the sensitivity of viral contaminates within the tissue to the inactivation methods tested; and 3) the extent of viral clearance observed in the study is significantly greater than the concentration of any pathogen present in the source tissue.

While data demonstrating the viral inactivation properties associated with manufacturing and sterilization processes are often determined in laboratory studies with the intended product, published literature demonstrating the viral inactivation parameters of device manufacture/sterilization processes may be submitted in lieu of such testing when appropriate. FDA recommends that literature information be submitted when: 1) the publication contains sufficient information to evaluate the study results (e.g., test conditions, sample composition, and the control studies performed to validate the test conditions); 2) information is provided which explains why the published test samples accurately reflect your product; and 3) information is provided which explains why the published viral inactivation procedures accurately reflect your manufacturing/sterilization methods (e.g., reaction temperature, solution pH and ionic strength, and time of product exposure to the inactivation step as well as the concentration of proteins and other impurities in your product and the cited publication).

Finally, please note that viral inactivation studies are not generally recognized to reflect the extent of prion contamination clearance or inactivation.

D. Transmissible Spongiform Encephalopathy-Specific Issues

BSE is a degenerative disease that affects the central nervous system of cattle and is similar to other transmissible spongiform encephalopathies (TSEs) found in sheep (scrapie), deer (chronic wasting disease),[16] and humans (Creutzfeldt-Jakob Disease or CJD and similar less common diseases). Current data suggest that the incubation period of two to eight years after exposure is required before BSE symptoms are detectable. Currently, there are no treatments for TSE diseases and no validated screening tests that detect infection in a live animal or human. Diagnosis is achieved by post-mortem microscopic examination of brain tissue, as well as assays using ELISA, Western Blot, or other techniques that detect abnormal forms of the prion protein.

The BSE infectious agent is widely theorized to be a prion (i.e., an abnormally folded form of a normal protease-sensitive cellular prion protein [called PrP^{C} or PrP(sen)]) that facilitates the

[16] USDA's Animal and Plant Health and Inspection Services website concerning CWD (Chronic Wasting Disease), available at https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/sa_animal_disease_information/sa_alternate_livestock/sa_cervid_health/sa_cwd

conversion of additional normal cellular proteins to an abnormal misfolded infection-associated protease-resistant prion structure (called PrP(res) or PrP^{TSE}). PrP(res) has been detected in bovine brain, spinal cord, eye, ileum, lymph nodes, proximal colon, spleen, tonsil, dura mater, pineal gland, placenta, cerebrospinal fluid, pituitary, adrenal, distal colon, nasal mucosa, peripheral nerves, bone marrow, liver, lung, pancreas, and thymus.[17] The detection of TSE infectivity in other tissues may occur in the future after data become available from more sensitive assays or larger animal studies. Transmission has been experimentally demonstrated in animal studies.[18] The TSE agent is known to be extremely resistant to traditional forms of disinfection and sterilization. Please refer to FDA's website regarding BSE, available at https://www.fda.gov/AnimalVeterinary/ComplianceEnforcement/BovineSpongiformEncephalopathy/ucm2006517.htm, for the most current information.[19]

Given the long incubation times before disease onset, the absence of a validated screening test for live animals, and vCJD's fatal outcome, we recommend that you collect and document the following information, in addition to the information listed in Sections A and B above, in your premarket submission for any material derived from ruminant animals (e.g., cattle, sheep, goats, cervids such as deer and elk) that have the potential to incubate a TSE infection:

- whether animals were sourced from a country with Negligible, Controlled or Unknown BSE risk (per OIE);[20,21]
- information concerning the long-term health of the herd (e.g., documented breeding history, animal traceability, absence of TSE disease and the surveillance program to detect a TSE);
- the animal feed composition (e.g., animal feed history records, including recordation of commingling of feeds, and labeling of animal feed composition at distribution locations) (note that in 2008, FDA issued a final rule prohibiting certain material from being fed to ruminants, see 73 FR 22719);
- the animal stunning and slaughter methods that reduce the risk of cross contaminating non-TSE tissues with material from tissues that could contain TSE; and
- the specifics of the ante mortem and/or postmortem inspections (e.g., gross visual inspection, specific organs and anomalies exams, lab tests such as PrP^{TSE} testing).

In addition, the manufacturing facility should document 1) procedures for maintaining records

[17] WHO Tables on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies (updated 2010), available at http://www.who.int/bloodproducts/tablestissueinfectivity.pdf

[18] Hamir, et.al., "Experimental interspecies transmission studies of the transmissible spongiform encephalopathies to cattle comparison to bovine spongiform encephalopathy in cattle." Journal of Veterinary Diagnostic Investigation, May 2011, 23(3):407-420

[19] Additional resources include World Organization for Animal Health (OIE) "BSE Situation in the world and annual incidence rate," available at http://www.oie.int/en/animal-health-in-the-world/bse-situation-in-the-world-and-annual-incidence-rate/, and "Variant CJD Cases Worldwide," available at http://www.cjd.ed.ac.uk/sites/default/files/worldfigs.pdf.

[20] "OIE List of Bovine Spongiform Encephalopathy Risk Status of Member Countries," available at http://www.oie.int/animal-health-in-the-world/official-disease-status/bse/list-of-bse-risk-status/

[21] 78 FR 72979

on the above cited items[22] and 2) all information outlined above on each lot of product manufactured (Device History Record).[23] If necessary to ensure the safety of the medical device, this information may be reviewed during inspection.

Furthermore, it is important to keep in mind that the residence time of TSE-infectious material on surfaces is unknown and methods to completely assure removal of TSE-infectious material from surfaces have yet to be fully defined. Cleaning processes developed to remove surface contamination in abattoirs after exposure to potentially TSE-infected animals (e.g., cattle, sheep, cervids such as deer or elk) may not have been fully characterized or validated for more critical sites or equipment used to manufacture devices. Therefore, for facilities involved in device manufacture using tissue from potentially TSE-infected animals, your documentation should also identify when/whether any potentially TSE-infected material may have been previously processed in the facility and what steps were taken to address any potential contamination. This information could include the information previously discussed under "Manufacturing Controls for Animal Tissue Components" in section IV.B. of this guidance and the dates of previous tissue processing (see also 21 CFR 820.50).

Because screening assays cannot ensure TSE-free tissues from cows or other ruminant animals, the methods discussed above (e.g., monitoring animal feed, controlling animal husbandry, and tissue handling) reflect the best available approaches for preparing safe medical devices from animal tissue. However, when a TSE-screening assay is validated to accurately identify TSE-contaminated tissues, FDA will consider revising this guidance as appropriate and recommending that such a test be introduced into the standard operating procedures for tissue collection and processing.

[22] 21 CFR 820.70
[23] 21 CFR 820.184