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

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Agenda

- Objectives
- Background
- Scope of the guidance document
- Topics covered in the guidance document
- How this affects stakeholders

Objectives

- Become familiar with the content of the revised final guidance document issued on March 15, 2019.
- Understand the difference between the previous final guidance document issued in 1998 and the revised final guidance document.
- Identify resources available to aid in preparation of submissions of medical devices with animal-derived materials.

Background

- The previous final guidance document on this topic was published in 1998 and addressed ways to specifically reduce the potential of exposure to bovine spongiform encephalopathy (BSE).
- The draft guidance for the revised final guidance document (“Medical Devices Containing Materials Derived from Animal Sources (Except for In Vitro Diagnostic Devices)”) was issued on January 23, 2014.
 - The draft guidance was revised to provide clarity on the following areas:
 1. The intersection between the standards and the guidance document;
 2. The information that should be documented in a premarket submission versus manufacturing facility records; and
 3. How to apply the Quality System Regulation.
 - Additionally, the specific benchmark for the sponsor to demonstrate a reduction of 6 logs of the viral load was removed. Now we recommend demonstrating that the sum of the log reduction is sufficient to produce a safe product.

Background

- The revised final guidance document (2019) is different from the existing guidance document (1998) as it:
 1. Provides recommendations related to viral pathogens and all transmissible spongiform encephalopathies (TSEs) not just bovine spongiform encephalopathy (BSE).
 2. Outlines information regarding animal sourcing and manufacturing that should be provided in premarket submissions and/or documented to file.
 3. Recommends how viral inactivation studies should demonstrate that the sum of the log reduction in virus of select processing steps and sterilization process(es) is sufficient to produce a safe product.

Definitions

- Animal: any vertebrate or invertebrate (including amphibian, arthropod [for example crustacean], bird, coral, fish, reptile, mollusk and mammal) excluding humans (*homo sapiens*)
- Ruminant: an even-toed ungulate mammal that chews the cud regurgitated from its rumen
- Transmissible agents: bacteria, mold, yeast, parasites, viruses, transmissible spongiform encephalopathies (TSEs) agents and unclassified pathogenic entities
- Inactivation: process by which the ability to cause infection or pathogenic reaction by a transmissible agent is reduced
- Non-viable: having no potential for metabolism or multiplication

Scope

The information in the guidance is applicable to all medical devices, except *in vitro* diagnostic devices and devices with animal materials generally recognized as safe (e.g., tallow derivatives), that contain or are exposed to animal-derived materials.

The guidance provides:

1. Information that the 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 the guidance;
3. Recommendations about how specific areas of Quality System Regulation should be applied to control and document the safe and consistent manufacture of medical devices containing animal tissue; and
4. More information on specific approaches for determining the ability of manufacturing methods to eliminate viral contamination in the final product.

Standard ISO 22442

- 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” provide recommendations for selection and handling of animal tissues as well as evaluating the risk of pathogen contamination in medical devices.
- FDA partially recognizes Part 1. Specifically, Clause 4.4.2 is not recognized
 - Clause states that if manufacturers cannot fully meet the requirements of ISO 22442-2, they may demonstrate the level of inactivation of transmissible agents (per ISO 22442-3) is sufficient.
 - FDA’s position is that the specifications outlined in both ISO 22442-2 and ISO 22442-3 should be met.
- FDA fully recognizes Part 2 and Part 3.

Control of Animal Tissue Collection

- The guidance document communicates the following recommendations for how the manufacturer should control animal tissue collection:
 1. Document the sourcing and handling of animal tissues, and
 2. Understand the capabilities of the manufacturing and sterilization processes to address the risks to patients.
- Premarket submission should include the following:
 1. Animal sourcing information that is consistent with standard ISO 22442-2,
 2. Tests performed for permitting tissue to be further processed and/or combined with other tissues and device components, and
 3. Material Safety Data Sheets.

Manufacturing Controls for Animal Tissue Components

In accordance with the Quality System Regulation, the manufacturing facility should document:

1. Procedures for maintaining records on the animal sourcing,
2. The information on animal sourcing provided for each lot of product manufactured, and
3. Methods for facility decontamination/sterilization to avoid cross-contamination.

Sterilization

- The validation of sterilization of devices containing animal tissue is complex and requires a case-by-case assessment.
- The guidance document references a series of standards (ISO 11135, ISO 17665, ISO 11137-1, ISO 11737-1 and -2, etc.).
- Other resources may include:
 1. For 510(k) submissions, please also refer to the guidance document “Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile.”
 2. For Premarket Approvals and De Novos, the general review process should be followed.

Validation of Viral Inactivation

- To ensure adequate inactivation and removal of viruses, the processing methods and sterilization techniques used in product manufacture should be assessed.
- Consistent with standard ISO 22442-3, the sponsor may either provide test reports for each manufacturing step that contributes to the reduction in the viral load or provide literature-based evidence for each manufacturing step.
- When a sponsor conducts testing to demonstrate viral inactivation of the medical device, the model viruses should be selected to reflect the actual viral contaminants that may be present in the source animal tissue (for example, DNA-based and RNA-based enveloped and non-enveloped viruses).

Validation of Viral Inactivation

- The results of viral inactivation studies should demonstrate that the sum of the log reduction in virus of select processing steps and sterilization process(es) is sufficient to produce a safe product.
- A final report should be included in the premarket submission with the following information:
 1. Animal species and tissue source material in the device as well as amount of virus(es) that might be present in the source material,
 2. Appropriateness of the model viruses selected,
 3. Relevance of 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.

Transmissible Spongiform Encephalopathy (TSE)



- There is no treatment for transmissible spongiform encephalopathy (TSE) diseases and no validation screening tests that detect infection in a live animal or human. Diagnosis is confirmed during post-mortem microscopic examination of brain tissue.
- The premarket submission for any material derived from ruminant animals should include the following:
 1. Whether the animals were sourced from a country or countries with negligible, controlled or unknown bovine spongiform encephalopathy (BSE) risk,
 2. Information on the long-term health of the herd,
 3. Animal feed composition,
 4. Animal stunning and slaughter methods that reduce the risk of cross contaminating non-TSE tissues with materials from tissues that may contain TSE, and
 5. Information about ante-mortem and post-mortem inspections.

Summary

- The guidance document will provide more clarity to the stakeholders in understanding what information should be submitted in premarket submissions related to medical devices with animal-derived materials, as well as what information should be documented in the manufacturing records.
- The guidance document helps manufacturers identify and manage the possible risks related to tissues from animal sources when these tissues are used in medical devices.

Resources

- The revised final guidance document may be found using this link:
<https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM381491>
- Standard ISO 22442 - Parts 1, 2, and 3
- ICH “Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin Q5a(R1)”

Questions?

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Recording will be available at:

<http://www.fda.gov/training/cdrhlearn>

Under Heading: Specialty Technical Topics;
Sub-heading: Animal Related Policy