

**FDA Webinar- Medical Devices Derived from  
Animal Sources Final Guidance Webinar Materials**

**Moderator: Irene Aihie  
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3:00 pm ET**

Coordinator: Welcome and thank you all for standing by. All participants will be on a listen-only mode until the question and answer session of today's call. At that time, you can press Star 1 to ask a question from the phone lines. I'd also like it to inform parties that the all is being recorded. If you have any objections you may disconnect at this time.

I'd now like to turn the meeting over to Ms. Irene Aihie. Thank you, ma'am. You may begin.

Irene Aihie: Hello and welcome to today's FDA webinar. I'm Irene Aihie of CDRH's Office of Communication and Education. On March 15, the FDA issued the final guidance titled, Medical Devices Containing Materials Derived from Animal Sources Except for Invitro Diagnostic Devices. The role of animal-derived materials in medical devices is well established. However, the use of animal materials introduces the risk of disease transmission from animals to humans.

The final guidance is intended to help manufacturers identify the possible risk related to tissues from animal sources when these tissues are used in medical devices. The guidance also provides recommendations on how to minimize these risks.

Today, (Scott McNamee), materials engineer in the Office of Compliance and (Angie Jain), Biomedical Engineer in the Office of Device Evaluation here in CDRH will discuss the final guidance. Following the presentation, we will open the line for your questions related to the information provided during the presentation. Additionally, there are other (unintelligible) subject matter experts here to assist with the Q&A portion of the webinar.

Now, I give you (Scott).

(Scott McNamee): Thank you, Irene. Good afternoon and thank you everyone for tuning in for our webinar. My name is Scott McNamee and I'm here today with Dr. Angie Jain to discuss the recently published updated guidance on the use of animal tissues in the manufacture of medical devices.

This is a look at what we'd like to cover today. We're going to cover the objective of the guidance, a little bit of how we got here, the scope of the guidance, how it covers what it does cover and the impact we believe this will have on stakeholders.

Primarily, we'd like everyone to become familiar with the updated guidance document. Also we hope everyone will come to understand the differences between the previous guidance document and this update. Finally, we'll identify some resources that are available to you as you prepare submissions for products that fall within the scope of this guidance document.

The previously published guidance document was released in 1998 and had within it the Center's understanding of how to address the risk to the public health from BSE, Bovine spongiform encephalopathy. Since 1998, a great deal has changed in our understanding of transmissible diseases and the

impact on the medical device market in particular from the use of materials derived from bovine animals.

A draft of an update was published in 2014. The document was revised to provide clarity on the intersection between recognized Standards in the guidance, what information should be documented in a premarket submission versus what information should be maintained in manufacturing facility records, and how to apply the Quality Systems Regulation. Also, the specific benchmark of six log reduction of the vital load was removed. Dr. Jain will speak in more detail about the current recommendations in a few minutes.

The final document has been edited in response to the feedback the Center received to the 2014 draft. Three of the key differences between this guidance document and the 1998 version are listed here. The guidance now provides recommendations regarding viral pathogens and all transmissible spongiform encephalopathies or TSEs not just BSE. It outlines the information needed related to the sourcing of animal materials and how that information should be provided and documented. It also recommends how viral inactivation studies should show the sum of the log reduction of viral load within the steps of the manufacturing process that will lead to a safe product for the market.

A brief interlude to discuss some of the definitions within this guidance document. These definitions have been taken from the ISO 22442 Part 1 Standard. For the purposes of this document, “animal” covers everything within the animal kingdom except humans. “Ruminants” are no longer just cattle. “Transmissible agents” are all the vectors of disease including TSE agents, viruses, bacteria, et cetera. “Inactivation” is how the transmissible agent is made safer or the ability to cause harm is reduced. And finally, “nonviable” is how we want these agents to end up, having no chance to survive or thrive.

The scope of this updated guidance document covers all medical devices of all classes that contain or exposed to animal-derived materials during their production, except *in vitro* diagnostic devices and devices containing or exposed to materials generally recognized as safe. We believe this guidance gives the users of the document: information important to documenting the safe and consistent manufacture of medical devices containing animal materials; how this information should be included within premarket submissions; recommendations regarding how certain parts of the Quality System Regulation should be applied to control and document safe and consistent manufacturing processes; and more information on specific approaches for determining how manufacturing processes can reduce or eliminate the viral load in the final product.

In response to the feedback received after the 2014 draft, the extent to which the Center recognizes the ISO 22442 series of Standards has been incorporated into the guidance document. That series of Standards addresses the application of risk management, controls on sourcing of animal materials, and the validation of elimination or inactivation of viruses and TSE agents.

Part 1 of the series is partially recognized. Specifically we don't recognize Clause 4.4.2 which puts forth an “**or**” proposition. We believe manufacturers should control the sourcing of the materials **and** address viral and TSE agent reductions through processing. Parts 2 and 3 are both fully recognized.

This updated guidance recommends documenting the source of the animal material and how that material is handled as well as understanding how the steps of manufacture can reduce risk to the public health from the use of animal tissues. Premarket submission should include the sourcing information outlined in Part 2 of ISO 22442, the tests results from processing controls of

the animal material and any MSD sheets, I'm sorry, Material Safety Data sheets, that may be available from component suppliers along the manufacturing process chain.

Within the records of the manufacturing facility, this guidance recommends procedures for maintaining the animal source records, information on animal sourcing for each lot of medical devices produced, and the methods for facility maintenance to control for cross-contamination.

Now I will turn the microphone over to colleagues, Angie Jain and she will speak in more detail about the recommendations within the updated guidance on the control of transmissible agents.

Dr. (Angie Jain): Thank you, (Scott). We will now discuss specific information that we recommend should be provided in your premarket submissions for devices containing animal-derived materials. First, we will discuss sterilization of the medical device containing animal-derived materials. Validation of the sterilization of the devices containing animal tissues is complex and requires a case-by-case assessment. The guidance document references several Standards as additional sources for further information which include ISO 11135, ISO 17665, ISO 11137 Part 1, ISO 11737 Part 1 and 2, as well as two to three additional standards referenced in the guidance document.

Other sources that we recommend you refer to are for 510(k) submissions, the sterility guidance document entitled "Submission and Review of Sterility Information and Premarket Notification 510(k) Submissions for Devices Labeled as Sterile." For premarket approvals, also referred to PMAs and De Novos, the general review process should be followed.

One of the concerns of using animal tissue as a material in medical devices is the potential for viral contamination which may negatively affect the patient. Therefore, to ensure adequate inactivation and removal of the potential viruses present in the animal source, the processing methods and sterilization techniques used to manufacture the device should be assessed which are referred to as a viral validation studies in the guidance document.

In the premarket submission, the sponsor may either provide test results for each manufacturing step identified to contribute to the viral inactivation or to the reduction in the viral load or provide the literature based evidence for each identified manufacturing step. This is consistent with Standard ISO 22442 Part 2. In the ICH entitled “Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin,” which is referenced in the guidance document, it recommends that “when viral clearance studies are being performed, it is desirable to assess the contribution of more than one production step to virus elimination.”

If you provide literature-based evidence, the manufacturing step identified should have similar model viruses and concentration of the reagent or sterilization set to demonstrate reduction of the viral load. When a sponsor conducts testing to demonstrate viral inactivation of the medical device, 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 envelope to non-enveloped viruses. Therefore we recommend at least four model viruses should be selected to demonstrate viral inactivation and the selected model viruses should be relevant to the species that is used as the animal source.

As (Scott) mentioned at the beginning of the webinar, one of the differences between the previous guidance that has been issued in 1998 and revised final

guidance document in March 2019, is that the results of viral inactivation studies should demonstrate that the sum of the log reduction in the virus of select processing steps and sterilization process(es) is sufficient to produce a safe product. In the issued guidance document, an example of six log reduction is noted.

A final report of the viral validation studies should be included in the premarket submission with the following information. One, animal species and the tissue source material in the device as well as the amount of virus or viruses that may be present in the source material. Two, the appropriateness of the model viruses selected, I mentioned this on the last slide that the model virus selected should be relevant to the animal species; therefore, we recommend that you include in the final report a justification as to why the model viruses were selected.

Three, relevance of conditions used in the virus inactivation studies to the commercial manufacturing methods. We recommend that during virus validation studies, manufacturers use the same conditions as in pH temperature, and concentration of the reagent. For example as what is used in the manufacturing processing step. And last but not least the final report should include why these studies demonstrate that the final product will be safe.

There is not treatment - as we mentioned previously at the beginning of the webinar, there is no treatment for TSE diseases and no validation screening tests that detect infection in a live animal or a human. The only full proof method of diagnosing whether an animal had a TSE disease is during postmortem microscopic examination of brain tissue.

Therefore premarket submission for any material derived from ruminant animals should include the following: One, whether the animals were sourced from a country or countries with negligible controls are unknown TSE risk. For example there are select countries that bovine material may not be imported into the United States; therefore, it is not recommended that bovine material harvested from the animal source from one of those countries.

Two, information on the long term health of the herd, Standard ISO 22442 Part 2 provides further information on the type of information that should be provided on the long term health of the herd. Currently, this part of the Standard recommends having at least eight years of information on the closed herd.

Three, animal feed composition, the animal feed should not contain tissue for remnant animals other than porcine and equine and that to the porcine and equine tissue should not - should be obtained from single species slaughter houses. Other options of animal feed may be vegetarian diets such as soy and vegetable-based feed.

Four, animal study and slaughter methods that reduce the risk of cross contaminating non-TSE tissues with materials from tissues that may contain TSE. Central nervous system tissues such as the brain and spinal cord is an example of tissue that may contain TSE. Therefore, typically to reduce the risk of cross-contamination, non-TSE tissues with TSE possibly contaminated tissue, they should be kept separately from the rest of the tissue. Information about antemortem and postmortem inspection should also be provided.

Just to summarize what we have discussed during this webinar, the guidance document will provide clarity to the stakeholders such as yourselves 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.

In terms of resources that you may use when preparing your premarket submissions, the revised final guidance document may be found using the link provided. You may also reference Standard ISO 22442 Parts 1, 2, and 3 and the ICH. If you have additional questions regarding animal sourcing manufacturing process or validation studies for preparing your premarket submission, you may submit a Q submission, which is also referenced in guidance document, and a link is provided to learn more regarding the mechanism to obtain FDA's feedback on your questions.

Further questions you may have may be directed towards Division of Industry and Consumer Education at FDA.HHS.gov. The slide presentation, webinar and transcript will be available at the following address: under heading specialty technical topics, subheading animal related policy.

Irene Aihie: And we'll now take questions.

Coordinator: Thank you. At this time if you would like to ask a question from the phone lines, please press Star 1. You will be prompted to unmute your phone and record your name. Please record your name so that I may introduce you for your question. Once again, it is Star 1 to ask a question. One moment for those to queue up.

(Scott McNamee): While we're waiting for the questions online to queue, one of the questions that has come up quite a bit with regard to this guidance is why did it take the

FDA so long to finalize this guidance? The FDA received so many comments from external stakeholders when they draft went out in 2014, all about this guidance. As a result underwent significant revisions in order to ensure that we were responsive to all the comments. And that's why it's taken this long. So hopefully in the end, excellent product.

Dr. (Angie Jane): Thank you (Scott). Another question that typically is asked is why did the FDA publish this guidance if there is already an international organization ISO Standardization? And how should industry interpret this Standard? With publication of the draft, the FDA has fully recognized ISO 22442 Part 3 and continues to fully recognize ISO 22442 Part 2. Currently the FDA partially recognizes Part 1 as was mentioned in the webinar by (Scott). Because the standard suggests that either knowledge of the tissue source or demonstrating adequate reduction of viral pathogens in the final product alone is sufficient to producing a safe product. The FDA's position as outlined in the guidance is that manufacturers should both document information regarding tissue source and demonstrate adequate reduction of viral pathogens in the final product. We have revised the guidance to be more specifically referenced, the intersection between the guidance and referencing series of standards.

Irene Aihie: We'll take our first question.

Coordinator: We do have a question from (Jane Arnold Round). Your line is open. (Jane) your line is open if you could check your mute button.

(Jane Arnold Round): Hello, can you hear me now?

Irene Aihie: Yes, we can hear you.

(Jane Arnold Round): Okay, thank you. Yes, I have a question about the substances that are regarded as, generally regarded as safe. And you mentioned at the beginning that there was an exception to those materials. Can you expand on that and in particular if we have a problem going through a PMA, what FDA would expect to see in terms of information on the animal material if it was generally regarded as safe?

(Scott McNamee): I think in the processing of materials that are generally regarded as safe, principally it has to do with tallow which is a material that was of concern initially because it is often sourced from cows. But once the processing that tallow goes through which is so extensive and quite (unintelligible), the consensus was that as a material that is used in the manufacturing of medical devices does not raise a risk of transmissible spongiform encephalopathies simply because of the extensive processing that the material goes through before it becomes tallow. Those materials I believe are outlined within the 22442 series as, in one of the appendices, I think. I am reaching back. It's been a while.

(Jane Arnold Round): Okay, so it would be specifically those materials referenced in the Standard?

(Scott McNamee): Yes.

(Jane Arnold Round): Yes, okay. Thank you.

Irene Aihie: We'll take our next question.

Coordinator: Our next question comes from (Val Ray). Your line is open.

(Val Ray): Hi, can you hear me?

Irene Aihie: Yes, we can hear you loud and clear.

(Val Ray): Thank you for the webinar. I guess my, and I'm representing Baxter. My question is kind of an offshoot of the previous one. And I understand that tallow derivatives, the harsh processing, but I'm curious about gelatin. Because gelatin is generally regarded as safe and also it goes through a similar harsh processing. So what's the FDA's stance on gelatin with regard to generally regarded as safe and animal origin?

Dr. (Angie Jane): Typically with medical devices that contain gelatin, we do request similar information that was outlined in the webinar. We do request the animal source information as outlined in Part 1 of ISO 22442. We also request the manufacturing process that you have used to produce your subject device and we also ask for viral inactivation studies to demonstrate that you have a safe product based upon the sum of a log reduction of the viral load.

(Val Ray): Okay and so -

Dr. (Angie Jane): And for example if you are obtaining the gelatin from a supplier, then we would request information from the supplier as to the information about the animal sourcing.

(Val Ray): And so then you're requesting different information than would be requested from ISO 22442? Because the least -

((Crosstalk))

(Val Ray): There's special consideration laid out in ISO 22442 for gelatin. And so if we're meeting those, then would we also be meeting the FDA's expectation? I believe that's an annex in Part 1.

(Scott McNamee): Is it a normative annex? If it's a normative annex then yes. If it's an informative annex then we should talk. Which is to say check with the folks who are reviewing the submission to make sure that everybody understands where the processing of that material plants.

(Val Ray): Okay. And this question was largely derived around the idea of the use of gelatin in plastics. So as part of the plastic and to part of the actual intended use of the product.

(Scott McNamee): When you say plastic, you mean in terms of packaging?

(Val Ray): No, as line an IV bag that contains the solution for example. The IV bag would let's say use gelatin in its production or a line or a set made of plastic but the intended use like the actual solution in the bag or what would be going through a line is not of animal origin.

(Scott McNamee): But the bag is. If it's still covered as a product that falls within our regulations, then it'll be subject to the scope of this guidance document.

(Val Ray): Thank you for the clarification. We just want to make sure that we're going to be doing the right thing.

(Scott McNamee): Thank you.

Coordinator: Once again as a reminder, it is Star 1 to ask a question from the phone lines. Next we have (Miriam) your line is open.

(Miriam): This is (Miriam). I had a general question. Material Safety Data Sheets from suppliers sometimes have statements such as materials of animal origin have not been introduced into the process and therefore have not been evaluated. What is the recommendation of the FDA when working with these suppliers respective of the guidance?

(Scott McNamee): Just so I understand, the Material Safety Data Sheet says that there are - that there have not been materials of animal origin introduced into the product?

(Miriam): Right.

(Scott McNamee): And is the product itself of animal origin?

(Miriam): Not that, no. There's (unintelligible) evaluation.

(Scott McNamee): I would think if the product is not of animal origin and the associated Material Safety Data Sheet indicates no materials of animal origin, then it would fall outside the scope of this guidance document.

(Miriam): Thank you.

Coordinator: With that, we're showing no further questions. I'll turn the meeting back over to Irene Aihie.

Irene Aihie: Thank you. This is Irene Aihie. We appreciate your participation and thoughtful questions. Today's presentation and transcript will be made available on the CDRH webpage at [www.FDA.gov/training/CDRHlearn](http://www.FDA.gov/training/CDRHlearn) by Wednesday, May 1. If you have additional questions about today's

presentation, please use the contact information provided at the end of the slide presentation.

As always, we appreciate your feedback. Following the conclusion of the webinar, please complete a short 13-question survey about your FDA CDRH webinar experience. This survey can be found at [www.FDA.gov/CDRHwebinar](http://www.FDA.gov/CDRHwebinar), immediately following the conclusion of today's live webinar.

Again, thank you for participating. This concludes today's webinar.

Coordinator: Thank you. Once again, that does conclude today's conference. Thank you all for participating. You may disconnect your lines at this time.

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