Medical Device Sterilization Town Hall: Sterilization Short Topics and Open Q&A
August 7, 2024

Moderator: CDR Kim Piermatteo

CDR Kim Piermatteo: Hello everyone, thanks for joining us for our tenth Medical Device Sterilization Town Hall. This is CDR Kim Piermatteo of the United States Public Health Service and I serve as the Education Program Administrator in the Division of Industry and Consumer Education, within FDA's Center for Devices and Radiological Health or CDRH. I'll be the moderator for today's town hall.

The FDA is committed to reducing reliance on ethylene oxide sterilization use while ensuring the integrity of the supply chain so that patients and providers have continued access to the sterile devices they need. To meet this goal, FDA continues to take a multipronged approach, including regulatory flexibilities, supply chain analysis and mitigation, collaboration, innovation, and communication, including this series of town halls.

I'd like to share a few administrative items before we get started today. First, please make sure you've joined us through the Zoom app, and not through a web browser to avoid technical issues. Next, trade press reporters are encouraged to consult with the CDRH Trade Press Team at cdrhtradepress@fda.hhs.gov. And members of national media may consult with the FDA's Office of Media Affairs at FDAOMA@fda.hhs.gov.

And lastly, for today's town hall we will begin with our segment on what we heard from you; then our panelists will provide discussions on three short topics; and then we will transition to our live question and answer segment where were look forward to interacting with you. If you have a comment or question, please wait to raise your hand in Zoom until we transition to this segment.

I now have the pleasure of introducing today's panelists; first, CDR Tamara Rosbury, Health Scientist and EtO Incident Response team member in the Division of All Hazards Preparedness and Response in the Office of Readiness and Response within CDRH's Office of Strategic Partnerships and Technology Innovation or OST; CDR Scott Steffen, Senior Program Management Officer and EtO Incident Lead in the Division of All Hazards Preparedness and Response in the Office of Readiness and Response within OST as well; Dr. Ryan Ortega, Regulatory Advisor on the Regulatory Policy and Combination Products Staff within the Office of Product Evaluation and Quality or OPEQ; Dr. Mitali Patil, General Engineer in the Office of Health Technology number two, for Cardiovascular Devices, in OPEQ.

Also joining us today is Dr. Anita Khatiwara, Biologist also in the Office of Health Technology number two, for Cardiovascular Devices, in OPEQ; Dr. David Craft, Microbiologist in the Office of Health Technology number three, for GastroRenal, ObGyn, General Hospital and Urology Devices, in OPEQ; and Jennifer Berg, Senior Staff Fellow in the Office of Health Technology number four, for Surgical and Infection Control Devices, in OPEQ as well.

Thank you all for serving as a panelist on our town hall today. I'll now turn it over to Tamara to start us off today. Tamara.

CDR Tamara Rosbury: Thanks, Kim. Thank you for joining us for our tenth Sterilization Town Hall. In today's town hall, our panel of sterilization experts will discuss topics on microbial test methods, followed by a live Q&A segment to engage with you and answer your questions. Before we begin, I'd like

to answer a few questions from our mailbox and then provide clarification on the purpose of the medical device sterilization mailbox.

Question number one, can you provide perspective on FDA engagement with other agencies, such as global health care agencies, and notified bodies on expediting regulatory approvals for changes in sterilization locations, cycle modifications, modality, et cetera?

Answer, FDA has been actively exploring where opportunities might exist, especially in areas where significant changes in regulatory requirements might be anticipated. We recognize that different jurisdictions may require the use of different technical standards. And some of our areas of engagement include our standards programs, participation in work groups, and recognition of sterilization standards to reduce overall regulatory burden.

Question number two, does FDA require a 30-day notice for addition of equivalent sterilization chambers in the same facility?

Per section two of our guidance, 30-Day Notices, 135-Day Premarket Approval (PMA) Supplements and 75-Day Humanitarian Device Exemption (HDE) Supplements for Manufacturing Method or Process Changes, a 30-day notice is used for changes to the manufacturing procedure or changes in method of manufacture. We encourage you to review this section for more clarity as it has some examples of appropriate changes for a 30-day notice that you might find helpful. If you need additional clarity, especially considering the specifics of the exact scenario you are considering, we recommend you contact your review division.

Question number three, what is the purpose of the medical device sterilization mailbox, and what types of questions should stakeholders submit?

Answer, the mailbox pertains strictly to content as it relates to the EtO Tiger Team Town Hall series. We use this mailbox to help determine discussion topics for future town halls and also to clarify topics already conveyed. We welcome your submission of questions and comments regarding medical device sterilization and topics that you would like to hear about.

Please note the following. We will aim to respond to questions and comments received in the mailbox in an upcoming town hall. Suggested content will be incorporated in our planning as potential future town hall topics. Questions about specific submissions or premarket applications should be directed to the appropriate review office. General questions regarding topics not brought up in the town hall series, including but not limited to medical device laws, regulations, guidances, and policies, covering both premarket and postmarket topics, will not be addressed during town halls. For questions regarding these topics, please contact CDRH's Division of Industry and Consumer Education, or DICE. Next slide, please.

We'll now take the opportunity to discuss a few short topics with our sterilization experts related to microbial test methods and what FDA reviewers look for during the review process. The short topics are shown here; these include testing considerations for bioburden testing, methods, and considerations for bacterial endotoxin, and testing considerations related to packaging integrity for sterile medical devices. Please note that assessments of adequacy are outside the scope of this town hall.

I will pass it to CDR Scott Steffen to get the discussion started on our first short topic.

CDR Scott Steffen: Thank you, Tamara. I'm really excited to discuss these topics today regarding bioburden monitoring, especially within the manufacturing paradigm. And keeping it to a minimum really facilitates sterilization, which leads me to our first discussion topic, which I'll start with Anita.

Anita, what is the bioburden, what is bioburden, and what are some considerations for testing the bioburden of a medical device? What methods and guidances are available? And lastly, what factors play a role in testing?

Anita Khatiwara: Thank you, Scott. Let us begin with a definition. So according to ISO 11737, bioburden is the sum of microbial contributions from a number of sources, including raw materials, manufacturing of components, assembly processes, manufacturing environment, assembly and manufacturing aids, cleaning processes, and packaging of finished products.

As we all know, the objective of a sterilization process is to destroy and permanently inactivate microorganisms or bioburden. And bioburden testing is performed to estimate the microbial load in the product. So, the test results from the bioburden can be used to determine sterilization modality and to select appropriate sterilization validation methods. So general definitions and recommendations for bioburden testing is outlined in ISO standard 11737 part 1 and 2.

CDR Scott Steffen: Thank you, Anita, for those definitions and recommendations. You just mentioned a couple ISO standards. Are these accessible to everyone?

Anita Khatiwara: Yes, Scott. However, they must be purchased from the standard organization, or one must have a subscription for the standard organization.

CDR Scott Steffen: Thank you for that answer. Follow-up question, is ISO 11737 FDA recognized?

Anita Khatiwara: Yes, Scott. All the standards we will be referencing today are either partially or fully recognized by FDA.

CDR Scott Steffen: Thank you. What about testing and documentation? Can you share with our audience any considerations?

Anita Khatiwara: Sure. So, some items to consider for your bioburden testing include test article. So, it needs to be a final finished product, that is, the product to have undergone all manufacturing and packaging processes but not sterilized.

Next consideration is sample size. The standard sample size recommendation for bioburden testing is between 3 to 10 samples.

And the most important aspect for bioburden testing is method validation. There are four aspects to consider for method validation, namely, the assessment of test method suitability, determination of bioburden recovery efficiency, assessment of suitability of techniques for the enumeration of microorganism, and, finally, assessment of the suitability of the techniques of microbial characterization.

Once the bioburden test method is validated and the associated recovery efficiency is established, it is used to determine the national bioburden of the final finished product for routine monitoring.

Mitali, would you like to add any considerations for bioburden testing or comment on the documentation reviewers look for in a marketing submission?

Mitali Patil: Sure, Anita. With regards to documentation, we look for in a marketing submission to include an executive summary with details of test methods used and test reports for bioburden method validation with corresponding recovery efficiency percentage calculations. The test report should also include methodology specifics, such as extraction volumes, extraction solution, time and temperature of extraction or incubation, and other such parameters. In addition, information on routine bioburden monitoring plans with established alert and action limits and descriptions of the actions taken when the limits are breached should be provided.

CDR Scott Steffen: Mitali, you mentioned routine. What defines routine monitoring?

Mitali Patil: That's a good question, Scott. Per section 8.8 of ISO 11737-1, in order to demonstrate that effective control of microbiological quality has been implemented and maintained, a program of monitoring the product and/or components should be developed. So, this monitoring is performed on a regular basis for routine determination of bioburden and interpretation of the results.

Sampling can be performed at a frequency based on time, for example monthly or quarterly, or on a production volume, for example looking at alternate batches. However, in order to establish baseline levels, it is a common practice to determine bioburden at a higher frequency during the initial production of a new product and then you can reduce this frequency as knowledge of the bioburden develops. Historical bioburden data is used to establish bioburden levels, and that is commonly defined as alert and action levels. Along with the establishment of these levels, procedures of steps or actions to be taken if the level is exceeded are to be considered. In addition, seasonal variations, such as humidity or temperature level changes, can also alter the types and numbers of microorganisms in the bioburden. So based on successive test results, bioburden data should be re-evaluated after a period of time to verify whether the original levels are appropriate.

CDR Scott Steffen: Yeah, thank you for that bioburden information. Are there any advantages to using a certain validation method when using this information?

Mitali Patil: There certainly are, Scott. With a better understanding of your product bioburden, you may be able to be more precise when determining your sterility assurance level. Therefore, with bioburden control and robust bioburden monitoring, you can open your options for sterilization. For instance, with radiation sterilization, product bioburden is an explicit consideration, so the bioburden will determine your sterilization dose. Whereas for gaseous sterilants, robust monitoring can support different validation approaches, such as biological indicator and bioburden approach or the bioburden-based validation methods. And these methods can support reduced concentration or more precise use of sterilant gases like ethylene oxide.

CDR Scott Steffen: Anita, getting back to you, you mentioned controls earlier. What type of controls should firms consider?

Anita Khatiwara: Sure, Scott. So, some of the controls include implementation of a validated bioburden testing method and having a robust monitoring plan in place. In addition, keeping track of changes that would impact bioburden, such as changes in manufacturing processes, water source, raw materials, supplies, et cetera, and also periodic re-evaluation of bioburden data to update alert and action levels as needed. Also, any changes to material and manufacturing process can impact validated bioburden recovery efficiency. Therefore, it is important to ensure that the new material and processes does not impact bioburden recovery, which needs to be verified by bacteriostasis, fungistasis, or B/F testing.

CDR Scott Steffen: Thank you for bringing up B/F testing. Could you explain what is bacteriostasis and fungistasis testing and why it should be performed?

Anita Khatiwara: Sure, Scott. So, B/F testing is also referred as method suitability test. It is performed to ensure that the device material does not impart any bacteriostasis or fungistasis properties to inhibit microbial growth. FDA recommends that B/F testing be performed in accordance with USP chapter 71, which recommends use of compendial microorganisms, which include aerobic and anaerobic fungi and spore farmers to fully assess the B/F properties. This test supports the results from microbiological tests such as sterility bioburden during validation testing. To support your marketing submission, B/F test reports with methodology specifics, such as microorganisms tested, inoculum size, culture conditions, and inclusion of positive/negative control, et cetera, needs to be provided for review.

CDR Scott Steffen: Yes, thank you, Mitali, and Anita, for that robust and informative discussion. I'm going to turn it over to Ryan Ortega to go through our next discussion topic. Ryan.

Ryan Ortega: Thanks, Scott. I appreciate the hand-off. So, for our next discussion, I'd like to dig into a topic that has some important implications for the safety of sterile devices and that's bacterial endotoxins. So, many sterile devices are assessed for the presence of bacterial endotoxins, such as those devices that are in direct or indirect contact with the cardiovascular system, the lymphatic system, or cerebral spinal fluid, implanted devices, or devices that have a nonpyrogenic labeling claim.

So now we'd like to talk about some of the considerations in bacterial endotoxin testing for these devices. For example, why is it needed? And what methods and standards are available? So, David, I think I'd like to start with you. Can you kick us off by telling us a little bit about what bacterial endotoxins are?

David Craft: Sure. So, pyrogens are any substance, either microbial or nonmicrobial, that can induce a fever. And certainly, bacterial endotoxins are microbial components of cell walls of gram-negative bacteria. These bacterial endotoxins can cause fever, meningitis, a rapid fall in blood pressure if introduced into blood or tissues of the outer body.

Bacterial endotoxins are ubiquitous in nature. They're stable, small enough to pass through conventional sterilizing filters, and can be released through both viable and nonviable bacteria. Therefore, testing for bacterial endotoxins is essential to understand the microbial pyrogenicity of any given medical device. Please note that this information presented today focuses on bacterial endotoxin testing, and it does not include material mediated pyrogen testing, which is a biocompatibility test that tests for pyrogenicity. Biocompatibility premarket expectations may be discussed later in a different town hall.

Ryan Ortega: Yeah, thanks, David. That's pretty critical background information and context for the rest of the discussion. Mitali, I think I'll go to you next. Are there recognized, FDA-recognized consensus standards that you could tell us about that someone could use to assess devices for the presence of bacterial endotoxin?

Mitali Patil: Yes, there are, Ryan. Thank you for asking. FDA recommends testing in accordance with the ST72-2019 standard, "Bacterial endotoxins, test methods, routine monitoring, and alternatives to batch testing." In accordance with this standard and consistent with FDA'S guidance, submission, and review of sterility information in premarket notification submissions for devices labeled as sterile, it's best practice to include particular information in the test report, such as a sampling or routine monitoring plan. For endotoxin testing, that sample size is typically dependent upon the lot size.

We also recommend including parameters that describe sample preparation and extraction procedures. This includes providing your maximum valid dilution calculations, the volume of water utilized for your extraction based on those calculations, and whether the sample was extracted by immersion or by flushing the device. Additionally, we ask that you please include the test parameters for extraction, such as temperature, time, and pH. We also request that you specify the test method used for endotoxin detection. This can include gel clot, chromogenic, or turbidimetric methods. And lastly, when providing the test report and the result summary, we ask that you please include your acceptance criteria, the level of endotoxins per device that is permissible, the test results, and any additional information associated with methods such as positive product control or coefficient of variation.

Ryan Ortega: Yeah, thanks, Mitali. So, it's good. It sounds like there are some very useful resources out there that can provide folks with some standard methods for endotoxin testing. David, going back to you, are there any other considerations that people should think about when they plan and conduct their endotoxin testing for their device?

David Craft: Yes, there are additional considerations for testing devices for bacterial endotoxins either prior to device sterilization or after device sterilization. Ideally, bacterial endotoxin testing would be performed on the final finished devices to ensure that all factors that affect the product or endotoxin test are assessed as endotoxin may be released from both living and nonviable bacteria. However, pre-sterilization samples may be selected if there is sufficient justification and documentation that the pre-sterilization sample endotoxin levels are representative of the finished sterilized product. This can be supported by pre-sterilization versus post sterilization bacterial endotoxin testing comparison across multiple lots and also by the assessment of materials, the manufacturing processes, and/or historical data for post sterilization bacterial and endotoxin testing.

Ryan Ortega: Yeah, thank you, David, for sharing some of those considerations. In the past, we've gotten questions from folks in industry about how often to conduct endotoxin testing or potentially what's expected for regular testing. So, I just want to check, does anybody have any final thoughts about routine endotoxin testing on device lots or batches or potentially alternatives to batch testing?

Mitali Patil: I can take this one, Ryan. Thanks for asking that question. Non-pyrogenicity is typically confirmed through the use of end-product batch testing for product release. So, we recommend following the table from Annex B in the ST72-2019 standard when generating your sampling plan. While alternatives to batch testing may be implemented, there are numerous factors that must be considered

before FDA can approve an alternative to batch testing. As such, you should work with FDA interactively or via a Pre-Submission to determine whether an alternative to batch testing is feasible for your device.

Ryan Ortega: Yeah, thank you, Mitali. And thank you, both, for providing your thoughts and insights on endotoxin testing. Now I'll turn it back over to Scott for the next discussion topic.

CDR Scott Steffen: Yeah, thanks, Ryan. Now let's move on to our last topic, package integrity. Sterilization can be engineered to be a very robust process. However, without a strong, sterile barrier, devices will not remain sterile after being sterilized. This really exemplifies the importance of a package's ability to maintain sterility and the importance of testing to demonstrate package integrity over time. Recognizing there is a variety of package integrity tests, what are the testing considerations related to package testing for sterile medical devices? Jennifer, why don't we start off with you?

Jennifer Berg: Sure, Scott. I'd be happy to. I'd like to provide some of the general requirements and definitions related to package integrity testing. But first, I think it's important to take a moment and talk about the types of packaging. There is often primary and secondary packaging for medical devices, with the primary packaging being what directly encompasses the medical device and often is what goes through sterilization. Secondary packaging may include boxes or other packaging that is not in direct contact with the device. Please note that the information we are providing here focuses on the primary packaging only.

Now I'll discuss some of the general requirements and definitions related to package integrity testing. This will include information from ISO standard 11607, "Packaging for terminally sterilized medical devices, what packaging is important, testing and sampling plans."

As per ISO 11607, the goal of a terminally sterilized medical device packaging system is to allow sterilization, provide physical protection, maintain sterility up to the point of use, and allow aseptic presentation. The sterility of a device is essential for ensuring patient safety for microbiological threats. Therefore, to ensure that the sterile barrier integrity is maintained throughout the manufacturing, distribution, storage, and shelf life of a device, validation is needed of the packaging system's sterile barrier. Package performance testing is meant to address if the sterile barrier can withstand stressors imposed by manufacturing or sterilization processes and environmental distribution or storage conditions.

Package stability testing is meant to address if the sterile barrier can be maintained throughout the shelf life of the device. There is also sample size considerations to think about. For marketing submissions, such as a 510(k), De Novo, or PMA, for example, it is important to select sample sizes that are commensurate with the level of risk to the patient if failure were to occur. A packaging failure can result in significant patient harm. We recommend a sample size is chosen that demonstrates the primary sterile barrier remains intact with 95% confidence, with 95% reliability.

CDR Scott Steffen: Thanks, Jennifer. Can you please explain the difference of ISO 11607 from testing standards?

Jennifer Berg: Sure. Thanks for that question. ISO 11607 is more of a high-level description of packaging and testing. It does not get into the specifics of how to perform the package integrity testing; however, ISO 11607 does mention a number of testing standards in Annex B.

CDR Scott Steffen: Thank you, Jennifer. Turning to you, David. Jennifer mentioned testing standards. Can you please provide an overview of package integrity testing?

David Craft: Sure. So, we refer to this as packaging performance testing. And ideally, this testing is performed on the final finished sterilized packaged devices. Just as a note, dunnage may be permissible if it is representative of the final finished device with respect to device geometry and weight.

So, after sterilization, the packaged system should undergo the following conditioning or testing, such as environmental conditioning according to ASTM D4332. FDA recommends using extreme cold, tropical desert conditions to assess the impacts of cold, humidity, and dry heat on the packaging system. Also, simulated distribution, ASTM D4169. For many devices, FDA recommends using the distribution cycle 13 at an assurance level of one or two to ensure that the impact of all modes of transport are sufficiently addressed. And then package validation testing itself could include visual inspection, according to ASTM F1886, where you actually visually inspect the sterile barrier for imperfections such as cracks, tears, folds, wrinkles that may result in a breach of the sterile barrier.

Bubble leak testing, according to ASTM F2096, which assesses the entirety of the sterile barrier for sources of leaks, such as pinholes, by submerging the entirety of the barrier under water. And then, finally, seal strength, according to ASTM F88, which assesses all seals of the sterile barrier for seal strength.

CDR Scott Steffen: Thanks, David. You mentioned a bunch of tests. Are these the only tests firms can use?

David Craft: No, not at all. This is, this is not an exhaustive list. And firms are not required to use these particular tests. For example, dye ingress, vacuum decay, package over pressurization, or burst testing could also be used.

CDR Scott Steffen: So, David, how can these tests be used to establish shelf life then?

David Craft: So, this is what we refer to as packaging stability testing. And again, this testing ideally should be performed on the final finished sterilized packaging. After sterilization, the packaging system should undergo the following conditioning and testing. Aging, which ultimately the sponsor should age the devices in real time up to the desired shelf life. And then, for most devices, it is permissible to perform accelerated aging at the time of marketing per ASTM F1980, which provides real-time aging and testing protocols for review and the premarket submission. And then either document the real-time aging results as an internal letter to file for such as 510(k) devices or an annual reportable change if it was a PMA.

And finally, this validation testing could include, again, visual inspection, according to ASTM F1886; bubble leak testing, ASTM F2096; and then seal strength according to ASTM F88. And again, the seal strength values from this stability testing and the packaging performance testing should be within one standard deviation of each other.

CDR Scott Steffen: Thank you for that. Does the agency have any recommendations or expectations for shelf life?

David Craft: No. No. The shelf-life determination is driven by the data. So, there is no expectations for any certain shelf life.

CDR Scott Steffen: Thank you very much for that, David. And Jennifer, appreciate your input as well. This was a very interesting discussion. Now, let me pass it to Tamara to provide references and a summation of what we just discussed today. Tamara.

CDR Tamara Rosbury: Thanks, Scott. Next slide.

The next two slides include the resources mentioned earlier in the presentation, along with the full URLs that you can access after the presentation.

We will summarize the discussion topics. Today's short topic discussion centered around microbial test methods used for medical devices that are terminally sterilized. We provided a brief insight on bioburden, bacterial endotoxin, and package integrity testing, including the following: considerations for testing when conducting bioburden tests on medical devices, testing considerations when evaluating bacterial endotoxin on medical devices, and testing for packaging integrity related to terminally sterilized medical devices. Next slide.

Before we open the discussion, I am excited to announce our next town hall on September 11, where our panel will discuss Sterility Master Files and Effective Use in Premarket Submissions. We'll include the live Q&A on topics identified by the audience and topics provided prior to the event via our medical device sterilization mailbox. Information about the town hall series can be found at the link here. Now I'll turn it back over to Kim.

CDR Kim Piermatteo: Thank you, Tamara. We will now transition to our interactive question and answer segment for today's town hall. I'd first like to go over how we will manage this segment and a few reminders.

So, to ask a question or provide a comment today, please select the Raise Hand icon, which should appear on the bottom of your Zoom screen. I'll then announce your name and give you permission to talk. When you're prompted in Zoom, please select the blue button to unmute your line. Please identify yourself and your organization and then ask your question or provide your comment.

If you have a question, please remember to limit yourself to asking one question only and try to keep it as short as possible. And then, after you ask your question and/or provide your comment and our panelists have addressed your question or comment, please lower your hand in Zoom. And then if you have another question or comment, please feel free to raise your hand again to get back into the queue, and I will call on you as time permits.

As we wait to receive some of your questions and comments today, I'd like to start us off with a few questions to our panelists. And the first question, I'll direct that to you, Jennifer. So, the question is, does endotoxin testing have to be performed if the sterilization validation was performed and demonstrated that no viable bacteria remained on the device through microbiological and physical performance qualifications and native product sterility testing?

Jennifer Berg: Thanks, Kim. Yeah, I can address that. While the sterilization validation, including the qualification testing and the native product sterility tests, are intended to demonstrate that no viable bacteria remain on the device, it is important to note that endotoxins are a nonliving component of gram-negative bacteria and are released once the gram-negative bacteria are destroyed.

As such, endotoxin release is independent of viability and should therefore be tested, even if your sterilization validation is successful and your native product sterility tests demonstrate no positive growth.

CDR Kim Piermatteo: Thanks, Jennifer. So, for our next question, I will direct that to Mitali. Mitali, the question is, can an alternative to batch testing be used for bacterial endotoxin testing instead of batch testing each product lot in order to release the lot?

Mitali Patil: Thanks for asking that question. While the standard for bacterial endotoxin testing does allow for alternatives to batch testing, we still strongly recommend proposing your alternative to batch testing plan via a Pre-Submission to determine whether you have enough information to support that alternative testing plan. Additionally, there are certain circumstances in which an alternative testing plan may not be ideal or feasible, so reaching out to FDA via that Pre-Submission prior to submitting an alternative testing plan will help us outline FDA's expectations for your particular scenario.

CDR Kim Piermatteo: Thank you, Mitali. David, I'd like to come to you next for another question. And David, that question is, does all device packaging need to be tested?

David Craft: So just a bit of clarity so packaging of medical devices can often consist of many pipes or layers. And so, often, there is a primary packaging that has direct contact with the device and the secondary packaging may include exterior wrapping or boxes that don't necessarily have direct contact with the device. The agency typically wants to see testing done on the primary packaging to ensure that the barrier is maintained throughout the established shelf life of the device.

CDR Kim Piermatteo: Thanks, David. Scott. Scott, I'm going to come to you for this last question before we take our first live question. And that one is for the last town hall, FDA demonstrated what a mock Pre-Submission meeting looks like. This was during our last town hall. So, what are the other types of Q-Submissions, such as a Submission Issue Request, or SIR? Or can you describe those other Q-Submissions?

CDR Scott Steffen: Yeah, I can. Thank you for that question. We get this question actually a lot, so it's really good that we bring this up. So, the short question, the short answer is that there is a lot of different types of Q-Submissions. The type of Q-Submissions are described in our guidance Requests for Feedback and Meetings for Medical Device Submissions, the Q-Sub program. And they include Submission Issue Requests, or SIRs, as was mentioned in the question, study risk determinations, and even informational meetings.

Interactions that are tracked through the Q-Sub program include PMA Day-100 Meetings, Agreement and Determination Meetings, submissions associated with breakthrough device, the Breakthrough Device Program, and the Safer Technology Program, or SteP, and Accessory Classification Requests are also included in this list of tracked submissions. Thank you.

CDR Kim Piermatteo: Thanks, Scott. Alright, I'm going to go to our first raised hand, and that is coming from Darren. Darren, I have unmuted your line. Please unmute yourself and ask your question or provide your comment to our panelists today.

Hi, Darren, are you able to unmute your line?

Darren Hopkins: I'm sorry. Can you hear me, OK?

CDR Kim Piermatteo: Yes, we can.

Darren Hopkins: OK, sorry. My name is Darren Hopkins. I'm a quality consultant for a small medical device startup and been doing work in the sterilization packaging for several years. And I wanted to talk about the last topic on shelf life. So, I thought I heard a comment around the results of shelf-life testing being within one sigma of, I what can't remember, either the real-time age or the T equals zero. Can you clarify that comment about the results of shelf life? What I'm used to seeing is either the pass/fail, like an attribute treatment of those shelf life results relative to spec. So let me know if there's anything else that you look to see in the results of shelf-life testing data. Thanks.

CDR Kim Piermatteo: Thank you, Darren, for that question. I'm going to go to David. David, would you like to start off by providing a response? And then any of our other panelists, feel free to chime in.

David Craft: Sure. I mean, I think, specifically, the business about the one deviation, the standard deviation would usually have to deal with something like seal strength. So yeah, I mean, that was, that would be where we would look at that for looking at any deviation from something that would be measurable in a sense that would have a value associated with it. Anybody else have thoughts?

Mitali Patil: This is Mitali. I would like to echo David's comments that seal strength is one of the variable measures in the packaging, in the packaging validation testing. So that standard deviation typically, that standard deviation requirement typically applies to seal strength or any other sort of variable parameters in your packaging validation testing. So typically, you would provide a specification, and then you need to be within one standard deviation of that. You would have to meet that specification. And then when you're asking about the within one standard deviation, it's really for comparing the baseline value of seal strength to your aged seal strength, be it real time or accelerated aged.

Darren Hopkins: OK, that makes sense. I appreciate your answer. Thank you.

CDR Kim Piermatteo: Thank you, Darren, for that question. And thank you, David, and Mitali, for your responses. Alright, our next question is coming from, I believe it's A. Rockwell. A. Rockwell, I have unmuted your line. Please unmute yourself and ask your question or provide your comment.

Amy Rockwell: Hi, my name is Amy. I'm calling in from Packaging Plans Labs. And our question is, is it considered mandatory or guided to have microbial IDs determined during each sterilization batch for a dose audit? Sorry.

CDR Kim Piermatteo: Thanks, Amy. I don't know if any of the panelists want to chime in at this point, or we can seek clarification from Amy's question.

Jennifer Berg: Sure. This is Jennifer. I can address that. I don't know if it's considered mandatory, but it is a helpful tool. Microbial characterization is often helpful to identify changes or trends in the product bioburden. Not only can you understand the types of microorganisms present, and it can also assist with identifying potential sources of contamination. And also, certain organisms may affect the sterilization process itself. So certain organisms may be resistant to your select sterilization modality and therefore may result in positive growth during your sterilization validation testing.

Amy Rockwell: OK, thank you very much.

Ryan Ortega: If I could add something there too. Hi, this is Ryan. That's a really good question, and it made me think about, I know that radiation is kind of a given that you're looking at the product bioburden as a part of dose setting. And so, I also think, though, if you're thinking about implementing like a BI bioburden or a bioburden-based method for some of the other, like a gaseous sterilant. And we've learned that using those methods can really result in very efficient or precise use of gaseous sterilants. I just think it could be useful, especially if you get a positive growth when everything's supposed to be dead.

To understand what might have went wrong, what sort of organisms are you looking at in terms of resistance. Conceivably if it is kind of a process concern or a deviation or a fail, then knowing what those organisms are, you might be able to tie it to, well, it's clearly something from the environment and the manufacturing facility, or it's something stranger that needs to be investigated, or maybe it's a seasonal variation. And so, while it's, like Jennifer said, it may not be mandatory, having that information can really help problem solve and also use some of the more precise and finer tuned, you might say, methods of validating cycles.

CDR Scott Steffen: Yeah, and if I may add on to what Ryan and Jennifer have said, Amy, one of the things I would point to back in our original discussion about bioburden monitoring, and it goes to exactly what Ryan was saying, and that's seasonal variation. So, depending upon the time of the year, your flora and fauna can actually change substantially. So that is something that you really want to take into account and make sure that you have a very robust system. And I think that that really goes to that fact of what Jennifer was saying and the fact that it is a very good tool and a very good research tool as you establish your sterilization processes among your facility.

So, a very robust bioburden monitoring system is a very good tool for this whole investigation that you're talking about.

Amy Rockwell: Awesome, thank you very much.

CDR Kim Piermatteo: Thank you, Amy, for that question. And thank you to our panelists for providing some commentary. Our next question is coming from Dominique. Dominique, I've unmuted your line. Please unmute yourself and ask your question or provide your comment.

Dominique, I see that you have unmuted your line, but we're still unable to hear you.

Dominique McNamara: Hi. Can you hear me?

CDR Kim Piermatteo: Yes, we can.

Dominique McNamara: OK, super. Sorry about that. Thank you, team. I just wanted to go back to a mention of devices that were required for testing for bacterial endotoxins. You mentioned that there was cardiovascular contacting systems, lymphatic system contacting devices. Were there any other special considerations for testing bacterial endotoxins for devices that are related to obstetrics use?

CDR Kim Piermatteo: Thank you, Dominique, for your question. I'm going to look toward David or Anita if you want to start with a response.

David Craft: Sure. So, I think looking at the guidance that's provided would be the best path for you to explore and to see what particular device that you're interested in and what the guidance would say about that, because that would be certainly something that we would use in our review process. Any other thoughts?

CDR Kim Piermatteo: Yeah, anyone else?

CDR Scott Steffen: I think just to reiterate the fact that there is a number of recognized standards that reference to endotoxin testing that could also provide some additional context to what your kind of looking for. It really is defined on, like you were saying, the exposure of the device and what symptoms, sorry, not symptoms, systems that are being exposed to that device. So, I would definitely encourage and echo what David said to look at those references there to make sure that whatever the device is in question is germane to those systems that would be at risk.

Ryan Ortega: And to add real quick, just some quick food for thought, I've actually got our 510(k) sterility guidance open in front of me, so that might be a useful tool. But there, we talk about how just some general guidelines, again, general, for endotoxin limits for things like general medical devices. So those would be like the blood contacting or implanted. Rule of thumb is maybe consider 20 endotoxin units per device, that's in our guidance. And then for things that are contacting cerebral spinal fluid or potentially the central nervous system, we recommend 2.15 EU per device as a starting point. But ultimately back to what's going to be appropriate for that specific device, for that specific intended use.

CDR Kim Piermatteo: Great.

Dominique McNamara: Sorry, I also just wanted to clarify. We've had recommendations from the administration for testing devices that are related to cesarean sections and obstetrics. And we haven't been able to find any definitive guidance as to why those devices specifically may need to be tested. As per the recommendations that we found, they haven't been falling into those categories per se. So, I just was trying to see if maybe there was any documents we might have missed, but maybe we'll just take a look back at that 510(k) that you mentioned.

Ryan Ortega: And I would also say reach out to the review division too if you've got specific questions about your specific case and your device.

CDR Kim Piermatteo: Great. Thank you so much, Dominique, for that question. And thank you, Ryan, Scott, and David, thank you so much for providing a response. Our next question is coming from Thuy Nguyen. I have unmuted your line. Please unmute yourself and ask your question or provide your comment.

If you have unmuted, I can see that you've unmuted, but we can still not hear you, so I don't know if you're double muted.

Thuy Nguyen: Can you hear me now?

CDR Kim Piermatteo: Yes, we can.

Thuy Nguyen: OK, I'm sorry. My name is Thuy Nguyen. I'm a compliance manager at a tissue banking manufacturer. My question is around the packaging integrity or performance. Is there a guidance around whether you should be testing at the max dose or the optimal dose? Or should there be a comparison across the dose, the radiation dose that's delivered to the packaging?

CDR Kim Piermatteo: Thank you for that question. Could you repeat, yeah, I know it was a little faint on our end. Can you talk up just a little bit louder?

Thuy Nguyen: Yeah, sorry about that.

CDR Kim Piermatteo: There you go.

Thuy Nguyen: OK, my question is around packaging integrity and performance of the packaging, whether we should be performing it at the max dose or the optimal dose range of the radiation? Or should there be a comparison across that as far as the integrity of the packaging?

David Craft: Well, typically, you would do the worst-case scenario for a lot of things. But this, again, this is just for packaging, but yeah, typically you would do it at the worst-case scenario just to make certain that you cover all the possibilities. Does anybody else have any thoughts?

Mitali Patil: This is Mitali. I'd like to echo David's comments that, yes, typically we do want to see worst-case radiation dosage. So it may be that you have a particular dose that you have used for your sterilization validation, but there might be a maximum threshold for that dose. So, you may want to test it at that maximum threshold just to ensure that the packaging integrity is maintained even at that maximum sterilization dose.

Thuy Nguyen: OK, thank you very much.

CDR Kim Piermatteo: Great, thank you so much for that question. Our next question is coming from Matt. Matt, I have unmuted your line. Please unmute yourself and ask your question or provide your comment.

Matt Wheaton: Hi, can you hear me?

CDR Kim Piermatteo: Yes, we can.

Matt Wheaton: Perfect. Hi, I'm Matt. I'm a quality engineer, and I was wondering, when we're evaluating packaging integrity per 11607, the testing recommended for the full sterile barrier system testing does not include any testing that can be validated for like a paper-paper porous packaging type

due to the porosity. Does the FDA have any recommendations on testing that can be completed on these packaging types that can fully confirm the sterile barrier system?

CDR Kim Piermatteo: Thanks, Matt, for your question. I'm going to open it up to our panelists. I know Jennifer or David; anyone feel free to chime in.

Ryan Ortega: Matt, that one may, unless anybody is very familiar with that specific testing, that may be specific enough to where we might have to look into that one. If we can't answer that here, would you be amenable to maybe sending that to our inbox? We can see if we can get you an answer there.

Matt Wheaton: Sure. Is it just the email that's down below?

Ryan Ortega: Yes.

CDR Kim Piermatteo: Yes. Yeah, the MedicalDeviceSterilization@fda.hhs.gov, yep.

Matt Wheaton: Perfect, thank you.

Mitali Patil: Matt, this is Mitali. I would also like to add that if you do feel that there are, that you do have a packaging system that does not necessarily meet the criteria to use the packaging validation tests outlined in the standard, you can definitely work with the review division via Pre-Sub to kind of determine if there is a test that you can perform, either one that you've sourced from a different standard that may not be FDA recognized or a method that's developed in-house. And you can work with the FDA in that review division via Pre-Sub to determine whether that method is feasible and how to sufficiently validate that method to ensure that you're maintaining the sterile barrier integrity.

Matt Wheaton: Thank you.

CDR Kim Piermatteo: Thank you, Matt, for that question. OK, I see no more raised hands at this time. I'll give it one more chance. OK, Elizabeth, you snuck in. I will unmute your line, and you can ask your question before we close today's town hall.

Elizabeth Jodon: Yes, it's a pretty simple question, I believe. I'm from Stryker. If you change the sterilization modality, does that generate an automatic requirement to change the part number of the product?

CDR Kim Piermatteo: Thank you, Elizabeth, for that question. Again, I'll just open it up to the panelists. Anyone want to provide a comment on, I believe, Elizabeth, it was changing the sterilization and having to change the part number?

Elizabeth Jodon: Yeah, is there a requirement to do so? If so, can you point us to the guidance for that?

CDR Kim Piermatteo: Sure. Anyone want to provide a general comment?

CDR Scott Steffen: Hi, Elizabeth, this is Scott. I'm going to just take a stab here in a second. What I would recommend you do is being, so we're all, some people are in specialized fields here, and some people are more general. Usually, the best course of action when you have a specific device space and a specific

device type, there might be some special considerations that review divisions actually know about that we wouldn't know about. That is, suffice it to say, that I think your best option really would be is to reach out to your review division and send them like a quick email and see what they have to say. And there's always the, there is always the option of a Pre-Sub if you wanted to bring that up. But I think just sending out a quick email just to kind of reach out and see what they think would be really the best course of action to get you the quickest answer possible. Thank you.

Elizabeth Jodon: Thanks.

CDR Kim Piermatteo: Thanks, Elizabeth, and thank you, Scott. Okay, so that will wrap up our question and answer segment for today's town hall. Thank you all for your participation. And at this time, I would now like to turn it back over to Tamara to provide her final thoughts for today.

CDR Tamara Rosbury: Thanks, Kim. Thank you for joining us for today's town hall and our panelists discussion about microbial test methods and for sharing your questions via email and during the live Q&A. We had great questions today related to a number of interesting topics. They include test acceptance criteria, criteria for seal testing, use of microbial IDs and sterilization batches and its use as a tool in sterilization processes, special considerations for bacterial endotoxins related to obstetrics use, thoughts on dose ranges for packaging integrity testing and to ensure integrity is maintained and identifying tests appropriate for paper due to its porosity for sterile barrier systems.

We are very much committed to continuing the dialogue on these critical medical device sterilization topics to try to make sure that patients and providers have access to the medical devices that they need. Thanks again for attending. And now I'll turn it back over to Kim.

CDR Kim Piermatteo: Thanks, Tamara. So, for me to close out today, for your information, printable slides of today's presentation are currently available on the events page for this town hall as well as CDRH Learn. And a recording of today's town hall and a transcript will be posted to the events page in CDRH Learn in the next few weeks. A screenshot of where you can find these materials on CDRH Learn is provided on this slide.

If you have additional questions or comments about today’s town hall topic, as well as if you have a comment or question for a future town hall, please email the medical device sterilization mailbox and that email is provided on the slide as well. And you can find a listing of all our upcoming medical device sterilization town halls and other webinars on our CDRH Events page, and that URL is provided on the bottom of this slide.

And lastly, as mentioned earlier, we hope you are able to join us for our next Sterilization Town Hall will be held on September 11, from 1-2 PM Eastern Time. And the potential for that topic is the sterility master files and their effective use in premarket submissions. So, we hope you are able to join us in September.

This concludes our town hall for today. Thanks again for joining us.

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