Medical Device Sterilization Town Hall:
Discussion of Premarket Submission Expectations and Additional Considerations for Sterility Review
February 7, 2024

Moderator: CDR Kim Piermatteo

CDR Kim Piermatteo: Hello everyone, and welcome to the third town hall in our series on the topic of Medical Device Sterilization. Thanks for joining us. This is Commander 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 in CDRH's Office of Communication and Education. I'll be the moderator for today.

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 multi-pronged approach, including regulatory flexibilities, supply chain analysis, and mitigation, collaboration, innovation, and communication, including this series of town halls.

Before we get started today, I wanted to share a few administrative items with you. First, printable slides of today's presentation have been posted to CDRH Learn. To obtain these slides you can go to CDRH Learn at www.fda.gov/training/cdrhlearn, and select the section titled Specialty Technical Topics and then the subsection titled Sterility. There you will find a section specifically for these medical device sterilization town halls and a link to the printable slides for today's town hall. Additionally, I encourage you to bookmark or remember this section in CDRH Learn because this is where we will post the recordings and transcripts for all town halls in this series. I'll repeat this information at the end of today's program as well.

Second, please make sure you've joined us through the Zoom app and not through a web browser to avoid technical issues. Third, 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, we look forward to interacting with you today. If you have a comment or question, please wait until we transition to the segment which follows the presentation to raise your hand.

I now have the pleasure of introducing our presenters for today's town hall. Dr. Lisa Simone, Senior Health Scientist and EtO Incident Lead in the Division of All Hazards Preparedness and Response in the Office of Readiness and Response within the Office of Strategic Partnerships and Technology Innovation, or OST. Christopher Dugard, Assistant Director in the Office of Health Technology Number 4, Surgical and Infection Control Devices in the Office of Product Evaluation and Quality, or OPEQ. And Dr. Shani Haugen, Assistant Director in the Office of Health Technology, Number 3, for Gastrorenal, OB/GYN, General Hospital, and Urology Devices in OPEQ as well.

Thank you all again for joining us. I'll now turn it over to Lisa to start today's presentation. Lisa.

Lisa Simone: Thanks, Kim. And thank you to everyone joining us today for our third sterilization town hall. Before we get started, we'd like to take the opportunity to answer some questions we received in our mailbox after our last town hall on January 26.

Question number one. Can FDA speak further on the co-packaging of sterile products mentioned during the January 10 town hall, and any opportunities with respect to EtO optimization?

Answer. To clarify, we were speaking of medical devices co-packaged into kits and trays. We're aware that kits can contain several different devices, with a wide array of materials and EtO may be the only modality that can sterilize these kits due to their broad material compatibility needs. We understand splitting kits could potentially increase logistical steps and inventory challenges, and we're interested in thoughts or experiences regarding the feasibility of separating components of existing kits or kitting devices in such a way that they may be compatible with other sterilization modalities or building kits after sterilization.

Question two. Can FDA provide some examples of where it is seeing speeding of approvals for sterilization changes?

Answer. FDA is unable to provide specific examples because that might disclose confidential information. However, we've gathered experience, for example, from the EtO master file pilot where master files are being used to make changes in sterilization modality without PMA supplements.

If you think there may be a shortage risk for your device or device type due to real or potential loss of sterilization capacity, our shortages groups would be interested in this information. In cases like these, we may be able to talk with you about mitigating potential shortages through regulatory flexibility on a case by case basis.

Question three. Is FDA still accepting applications to the EtO master file pilot program?

And the answer is yes to all three pilot programs. The EtO sterilization, the 510(k) sterility, and the radiation sterilization master file pilot programs that we discussed in the last town hall. These are all still open to participants. If you think you might want to be involved in one of these pilots and have questions, you can reach out to us at CDRH-Innovation-Sterilization@fda.hhs.gov.

Question four. Has FDA considered opportunities where a predetermined change control plan, or PCCP, could be an avenue to assist in sterilization changes?

And the answer is, FDA has authority to authorize predetermined change control plans for specific modifications that would typically require a new PMA supplement or 510(k). The PCCP would allow for the implementation of these specific modifications without the need to submit a future premarket submission. This applies to any device type, and the PCCP would need to ensure that the device remains safe and effective when the proposed modifications are implemented. Generally, FDA believes that certain sterilization changes could be appropriate for a PCCP; however, this would depend on the specifics described in your PCCP. We encourage you to submit a pre sub to your relevant review team to discuss the appropriateness and the content of your proposed PCCP.

And finally, we received several questions about the logistics for this town hall series, so I'll, answer them together.

We do aim to provide announcements one week before each town hall. Our sterilization website, which will be shown in a later slide, does list the initial five town halls by date, time, and tentative topic area.

After the presentation, Kim will share how to access the slides in the video and the transcript, as she mentioned on the first slide if you aren't able to attend these live events. And to be notified of future events, please consider subscribing to our CDRH new mailing list. You can find our news and updates web page by searching for C-D-R-H-N-E-W.

Finally, submitting questions completely anonymously is not possible; however, we don't share attribution for emailed questions that we discuss during this portion of the town hall. For questions asked later during the live Q&A, our moderator Kim will use whatever name information has been entered into Zoom. There are some additional questions, but in the interest of time we'll save those for the next town hall, or if we have time available at the end of today's Q&A session. Next slide, please.

We've shared this timeline with you previously, and today's topics will include two of the items highlighted in yellow. Last year's new standards recognition and the recent revision of the 510(k) Sterility Guidance in January. Next slide, please.

Today's town hall on medical device sterilization will focus on sterility reviews and additional device and submission considerations. Our learning objectives for today are to understand FDA expectations for premarket submissions based on the 510(k) Sterility Guidance, including recent guidance changes, sterilization modality categories, and what to include in a submission. And to understand additional device and submission considerations for sterility that impact FDA review. And now I'll turn it over to Chris Dugard for the next learning objective.

Christopher Dugard: Thank you, Lisa. So as noted by the learning objective, I will be covering expectations and submissions. Next slide, please.

Thank you. So, the primary focus of this presentation will be on information to submit in a 510(k), which is covered in this guidance. Submission and Review of Sterility Information in Premarket Notification 510(k) Submissions. We will also cover the high level differences between submitting for a 510(k) and what to submit for IDE or PMA submissions. This presentation will not focus on our review of validation reports or what should go into a validation report. In addition, for device specific concerns, we encourage you to reach out to the respective OHT.

To start, I'd like to describe what is within scope of this guidance. So, the scope of this guidance is limited to the review of 510(k)s for devices labeled as sterile that are subject to industrial terminal sterilization processes based on microbial inactivation.

Issues that are outside of the scope of this guidance include sterilizers that are themselves medical devices subject to 510(k), for example, tabletop health care sterilizers; microbial exclusion processes, for example, filtration or aseptic processing, rather than microbial inactivation processes; processes intended to sterilize medical devices that incorporate materials of animal origin; processes that incorporate the use of liquid chemical sterilants; processes intended to be used by reprocessors of single use devices; cleaning, disinfecting, and sterilizing information for reusable devices that are reprocessed at health care facilities. And many of those are covered in separate guidances that are not part of this particular town hall. Next slide, please.

So since this is quite relevant to this presentation, we wanted to mention that we recently published an update to this guidance where we recognized vaporized hydrogen peroxide as an established category A

modality. This is thanks to our recent May 2023 recognition of ISO 22441, which is specific to vaporized hydrogen peroxide. I will discuss the specifics of what the various categories mean and how they impact what you should submit in a later slide. However, I did want to mention that we have also included a note in our recognition, and this note states, "Defined critical parameters can vary depending on the technology and cycle design of various vaporized hydrogen peroxide sterilizers. If you are considering releasing product loads using parametric release, please pay attention to process variables to monitor when releasing product loads using parametric release. We encourage you to contact the review division for your device regarding the appropriate parameters to monitor for parametric release of product load sterilized or vaporized hydrogen peroxide." The primary reason for this note is to ensure the appropriate critical parameters are monitored if parametric release is chosen, since as noted in the note, vaporized hydrogen peroxide sterilizers can vary greatly in their cycle design. Next slide, please.

So I'd like to discuss the different categories we've identified for the various modalities. For the most commonly used sterilization methods, there have been decades of research to understand those processes so that the sterilization process can be adequately controlled and monitored to reproducibly sterilized products. Based on this research, we understand how the sterilant behavior might be impacted by different conditions, what the most important conditions in the sterilization process are, the hardest to kill microorganisms for that process, the mathematical relationship between microbial kill and exposure to the sterilant, and we have an understanding of the material compatibilities with the sterilization process.

So, using that information, standards groups have identified validation methods for the most commonly used modalities, and those validation methods are described in FDA recognized standards. So what that means is that for 510(k) submissions, we have divided the modalities based on the agency's familiarity with them. I'll go into more details in the subsequent slides, but in general, category A is for those methods that the agency is very familiar with, in other words, they have a recognized standard. Established B are modalities we have some familiarity with but may not have a recognized standard. And novel methods are those that we have limited experience with. Next slide, please.

So established category A methods are methods with a long history of safe and effective use, and we have a lot of experience with them. We see them a lot in regulatory submissions. There's a lot of scientific literature out there regarding these methods, and there are recognized consensus standards to support the validation and use of these methods. Here on this slide, we have some examples of established A modalities.

Dry heat is fairly straightforward. The device load is kept in a chamber at fairly high temperatures for a certain amount of time. Steam or moist heat is similar in that it is a heat based method, usually conducted in a large chamber, but there are additional considerations, like pressure control to ensure the steam quality is maintained. Ethylene oxide, or EO sterilization, is a chemical-based method. Most EO sterilization methods expose a sterilization, a sterilized load to EO gas in a large chamber, where things like pressure and temperature are tightly controlled. Radiation methods are a little different than the other methods in that they tend to use a conveyor system to convey a sterilization load through a radiation source. Different sources can be used, but the overarching idea is that you pass the load through the radiation emitted by the source in order to achieve a certain radiation dose throughout the load. Vaporized hydrogen peroxide is the latest modality to be added to this list. As the name implies, it utilizes vaporized hydrogen peroxide to sterilize devices, and sometimes plasma is used to aid in removal of the sterilant from the chamber. So, we've seen that roughly half of all sterile medical devices

are sterilized using EO, and about 40 to 45% are sterilized with radiation, with the other modalities making up the remainder. Next slide, please.

Established B methods are methods for which there are no FDA recognized dedicated consensus standards, but for which published information on development, validation, and routine control is available and FDA has previously evaluated sterilization development and validation data for specific sterilizers using discrete cycle parameters and determined the validation methods to be adequate. By dedicated consensus standard, we simply mean a standard focused on a specific modality. For example, the broad sterility standard is ISO 14937, which can be used in conjunction with a modality specific standard, such as the recently recognized vaporized hydrogen peroxide standard, ISO 22441. We don't have a lot of examples of these, but flexible chamber systems are often considered established B methods. Next slide, please.

And finally, novel modalities. These are newly developed methods for which there exists little or no published information, no history of FDA evaluation of sterilization development and validation through a cleared 510(k) or approved PMA for devices sterilized with such methods, and no FDA recognized dedicated consensus standards on development validation and routine control. Some examples include chemicals that have not been cleared or approved by FDA as a sterilant or haven't been identified in scientific literature as a sterilant, a novel combination of chemicals, modified cycles of an FDA cleared health care sterilizer that have not that have not been previously reviewed. And some specific examples may include vaporized peracetic acid, high intensity light, or pulsed light, microwave radiation, sound, or UV light. Next slide, please.

Alright so here's the basic information of what you will need to submit in a 510(k), and some of this will be expanded on a little bit in subsequent slides. So sterilization method or modality is very straightforward. The maximum level of residuals remaining on the device with the associated limit, if this is applicable. This would be applicable for any chemical sterilization method. Radiation dose. Again, if applicable. Standards followed and validation methods used. For example, overkill or the BI bioburden method. Product adoption is often seen and is acceptable, provided adequate justification and adoption assessment is included. Sterility assurance level, which we typically see in SAL 10 to the minus 6, but alternate SALs have been used as well but should be discussed with the agency prior to submission. Pyrogen information. In other words, endotoxins. The limit depending on the risk and contact classification of the device. For this, we would like to know the method used and evidence that the endotoxin levels are below the specified limit, as well as a testing plan. And note we typically expect lot to lot testing, but alternate testing plans can be discussed. A packaging description and shelf life testing. Described generally, the packaging system. For example, as a heat sealed tieback, a thermoformed tray, et cetera. And performance related to shelf life and maintenance of the sterile barrier.

For established B modalities, some additional information may be requested, 510(k) clearance number, make and model of the sterilizer, and cycle information if applicable, and identification of prior premarket review, in which the sterilization method and cycles were evaluated, is all useful information that will support your submission.

Full test reports will be needed for novel modalities, including information supporting the proposed monitoring accessories. For example, justification of your select, your selection of most resistant organism, sterile barrier, et, cetera. And this is highly encouraged that you discuss with the agency prior to submission. Next slide, please.

So now we'll discuss what you need to submit for submissions other than a 510(k). For PMAs or De Novos, or IDEs, excuse me, full test reports are needed. A full test report includes objective of the test, description of the test methods and procedures, study endpoints, predefined pass/fail criteria, results summary, and conclusions. In terms of sterility, a full test report will include installation qualification, operational qualification, and performance qualification. This includes all microbiological testing, biological indicator resistance characteristics, residuals, et cetera.

So, for IDEs, full test reports may be needed but batch release testing or a sterility test is performed on units pulled from sterilized lots is acceptable. The agency only needs assurance the patients in the study will be using a sterile device, but full production validation is not needed. So, with that, I will pass it to Dr. Shani Haugen to discuss additional considerations. Thank you.

Shani Haugen: Thank you, Chris. Next slide.

I'll be discussing additional device and submission considerations that impact FDA's sterility review. Next slide.

Residual ethylene oxide limits are impacted by the contact classification of the device, the patient population, and the specific device type. FDA recognizes ISO 10993 part 7, which describes test methods and allowable limits for ethylene oxide residuals. Contact classification refers to the duration of exposure of the device to the patient. Permanent, prolonged, or limited. Evaluation of ethylene oxide residuals should also consider tolerable contact limit to prevent localized irritation due to ethylene oxide residual release from the device. In 2019, ISO 10993 part 7 was amended to consider allowable limits for devices used with neonates and infants, meaning there are lower limits for devices specifically indicated for or well understood to be used with neonates and infants.

Device manufacturers should also be aware of limits for specific devices, such as extracorporeal blood purification devices. Refer to section 4.3.6 of the standard or applicable device specific guidance documents or special controls or discuss with your FDA review team for information on device specific ethylene oxide residuals. Next slide.

Pyrogen testing is conducted for devices based on the type of patient contact made and the labeling. Implants, as well as devices in contact, directly or indirectly with the cardiovascular system, the lymphatic system, or cerebrospinal fluid, including devices that are present for similar systemic exposure, should be tested to meet pyrogen limits. In addition, any devices labeled non-pyrogenic should also be tested to meet pyrogen limits. Support that a device is non-pyrogenic typically includes two different tests. An endotoxin test such as the limulus amebocyte lysate, or LAL assay, usually conducted on every lot of product and a material mediated pyrogenic test, such as the rabbit pyrogen test that is typically conducted once and is part of the biocompatibility testing.

Premarket submissions should include an explanation supporting the endotoxin limit. For most non-cryogenic devices, the limit is 20 endotoxin units per device; however, devices that contact cerebrospinal fluid have a limit of 2.15 endotoxin units per device. And different devices may have even lower endotoxin limits, such as certain ophthalmic devices. Please refer to applicable FDA guidance documents and standards to understand if your device has a device-specific endotoxin limit. You can also refer to USP 161, ANSI/AAMI 72, and USP 85 for information about endotoxin testing. FDA also has

a 2012 guidance document titled "Guidance for Industry, Pyrogens and Endotoxins Testing, Questions and Answers" that has helpful information about pyrogen and endotoxin testing. Next slide.

Sterility review in a premarket submission also addresses packaging and the maintenance of the sterile barrier packaging over the shelf life. In a 510(k) submission, submitters should provide a description of the primary packaging, meaning the sterile barrier, and a description of the package test methods, but not package test data. In a 510(k), submitting declarations of conformity to the ISO 11607 standards is sufficient to describe the package test methods.

In a 510(k) submission, the shelf life of a device addresses both the maintenance of the sterile barrier packaging over the duration of the shelf life and performance testing of the aged product. Performance testing of the aged product should be addressed in the performance testing section of the 510(k) submission. To support shelf life of the sterile barrier packaging, packaging tests such as seal strength are conducted on accelerated aged or real time aged packages. For more information on accelerated aging, please refer to ASTM-F 1980. In contrast to 510(k) submissions, PMA and De Novo submissions should include complete test methods and data for both packaging and shelf life. Next slide.

We wanted to address two questions that frequently arise from device manufacturers. The first is, what sterility attachment should I provide for my eSTAR 510(k) submission?

Well, most sterile devices are subjected to an established A sterilization method and the sterilization cycle is validated in accordance with FDA recognized standards. For those 510(k) submissions, although eSTAR allows you to attach multiple documents, you typically will not need to provide additional attachments other than pyrogen information, or perhaps if there's a device-specific guidance document or special control that identifies specific sterility information to be provided.

For all the other sterility information recommended in the 510(k) Sterility Guidance, and again, this is for an established A sterilization method, eSTAR will prompt you to input that sterility information in eSTAR itself. So, in this scenario, there is no need to provide sterilization validation reports or packaging test reports. However, if your device is sterilized by an established B sterilization method or a novel sterilization method, or if you are not validating your cycle in accordance with FDA recognized standards, then you should attach the additional information that is recommended in the 510(k) Sterility Guidance.

So, to recap, if your 510(k) device is subjected to an established A sterilization method and the cycle is validated in accordance with FDA recognized standards, then the only sterility attachments to eSTAR should be for pyrogen information, if applicable, and addressing any device-specific sterility recommendations.

We also wanted to address adoption of devices into a validated sterilization cycle. Device manufacturers frequently ask, what adoption information should I submit in the 510(k)? Well unless there's a device-specific need to provide sterilization adoption information, you do not need to provide adoption information in a 510(k) for a device sterilized using an established A method, validated in accordance with FDA recognized standards.

We're bringing these questions up because we have observed a trend of device manufacturers submitting unnecessary sterilization information in 510(k)s. However, if you provide information beyond

what is recommended in the FDA 510(k) Sterility Guidance document and if that information raises patient safety concerns, so for example, you state that you're providing complete sterilization validation reports, but the reference reports are merely tests for sterility, that may prompt additional questions from us to ensure the safety of the device. The least burdensome approach for both industry and for FDA is to follow the policies we've laid out today and only provide information that we need to complete the 510(k) sterility review. 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. Next slide. And next slide.

So to summarize, we describe the sterility information expected to be in premarket submissions. We described the recent revisions to the 510(k) Sterility Guidance. We compared the three different sterilization categories and how they impact the level of information that should be provided. And we explained additional considerations about your device or submission that may impact the information that should be provided. Next slide.

Before we open up the discussion, we're excited to announce our next town hall on February 29, where we plan to discuss premarket considerations for modifications to sterilization related submissions and use of device master files and the sterility master file pilot programs in sterility reviews. Information about the town hall series can be found at the link on this slide. Now I'll turn it back over to Kim. Thank you.

CDR Kim Piermatteo: Thank you Shani, and thank you Lisa and Chris for your presentations today. We will now transition to our interactive comments and question and answer segment for today. Joining our presenters today as part of this segment, we have Dr. Suzanne Schwartz, Director of the Office of Strategic Partnerships and Technology Innovation, or OST. Dr. Ryan Ortega, Regulatory Advisor on the Regulatory Policy and Combination Product staff within the Office of Product Evaluation and Quality. And Dr. Aftin Ross, Deputy Director of the Office of Readiness and Response within OST. Thank you all again for joining us.

Before we begin, I'd like to go over how we will manage this segment, and a few reminders. To ask a question or provide a comment, please select the raise hand icon, which should appear on the bottom of your Zoom screen, I'll announce your name and give you permission to talk. When prompted, please select the blue button to unmute your line, identify yourself and your organization, and then ask your question or provide your comment. If you have a question, please remember to limit your question, please remember to limit yourself to asking one question only and try to keep it as short as possible. After you ask your question or provide a comment, please lower your hand and if you have another question or comment, please raise your hand again to get back into the queue and I will call on you as time permits.

Now as we wait to receive some of your questions and comments regarding today's topic, I'd like to circle back to our additional panelists for a few questions.

For our first question, I'll be directing that to Suzanne. Suzanne, the question is, what has been the overall response from external stakeholders about the update to the 510(k) Sterility Guidance?

Suzanne Schwartz: Thank you, Kim. The overall response has been very positive. We've seen an uptick in press, trade press, immediately after our announcement. And we're very hopeful that firms are going to find this change to be beneficial to them, as well as least burdensome. I want to also make sure to encourage stakeholders to reach out to us with ideas on how we can continue to help, through town hall, as well as other mechanisms. So, a great way to convey this information would be through our medical device sterilization mailbox and again, that mailbox is medical device sterilization, one word, at fda.hhs.gov (MedicalDeviceSterilization@fda.hhs.gov). Thanks.

CDR Kim Piermatteo: Thank you, Suzanne. Alright, next, Aftin I'm going to come to you with a question. The question is last town hall a live question was asked about FDA's thinking about removing paper-based materials from the ETO load, in other words, IFUs that do not require sterilization. Can you share more?

Aftin Ross: Thank you, Kim. So, we've received similar questions to our mailbox as well, and they mentioned the potential immediate benefit to reducing the amount of ETO use. As we shared last time, we're looking for device areas where an impactful reduction in ETO might be possible. For example, section 502F of the Food, Drug, and Cosmetic Act allows required labeling for prescription devices intended for use in health care facilities, or by a health care professional, and required labeling for in vitro diagnostic devices intended for use by health care professionals, or in blood establishments, to be made available solely by electronic means, provided that the labeling complies with all applicable requirements of law and that the manufacturer affords such users the opportunity to request the labeling in paper form.

It's noted that any information you provide to us via the mailbox is considered confidential proprietary, and it would be protected in accordance with applicable law. We would only use it to augment our understanding of the current challenges and successes with electronic labeling. With that in mind, we're interested in the following. First, if you are using paper labeling for ETO sterilized devices where the statute permits, electronic only, have you ever considered shifting from paper labeling to e-labeling as a risk mitigation measure for ETO reduction? If so, what are the strategies or best practices you've considered, and are there any challenges or showstopper issues to be aware of? For those who might have already shifted to e-labeling for ETO sterilized devices where permitted, we are looking for insights on whether you saw a reduction in ETO use, and if so, what types of devices? In addition, if there were any strategies or best practices that you considered as you made that transition? And what, if any, challenges you face as part of that transition. Thank you.

CDR Kim Piermatteo: Thank you, Aftin. Alright for our next question, Ryan. The question I have for you is, do you accept promissory notes?

Ryan Ortega: Yeah. Thanks, Kim. This is an important one, I think, because we do see this on occasion. What's usually meant by a promissory note in this context is that's when there's maybe a statement in a premarket submission that says a certain test, in this case, let's stick with sterility, a certain test will be performed prior to marketing the device, rather than conforming, I mean confirming that it's already been performed, and then giving the results in that submission for FDA to review. An example of this might be a promissory note in the sterility section of a submission. It could say something like, the manufacturer is saying we will validate the sterilization process to an SAL of 10 to the minus 6 in accordance with such and such sterility standard. And in general, we don't accept promissory notes. Going back to that example, we would expect that the sterilization process would have been validated

before the premarket submission is given to FDA for review and that all of the appropriate validation information is included in that submission, you know, according to the submission type, as Chris had outlined previously.

CDR Kim Piermatteo: Thank you, Ryan. Okay at this time, we will now hear from our first live audience member. That is going to come from Joan. Joan, I have unmuted your line. Please unmute yourself and ask your question.

Joan Melendez: Good afternoon, everyone. Thank you so much for having these conversations. You guys are amazing. I have lots of questions, but I'm going to limit it to one. Really talking about the IFU, the instructions for use. What are your thoughts about really supporting it a little bit better? We're seeing a lot of issues in the market where the IFUs of manufacturers are being copyrighted and then held into repositories or IFU libraries and they're becoming outdated because the hospitals can't get them directly from the manufacturers. So how are you-- how are the manufacturers strengthening their IFU for more of an electronic access to come up like more with the regulations in the EU? Thank you so much.

CDR Kim Piermatteo: Thank you Joan for your question. So, I'm looking at Shani or Chris, did you want to talk to a little bit about the IFU and availability?

Aftin Ross: Hi, this is Aftin. Oh, go ahead.

Christopher Dugard: Thank you, Aftin. Go ahead, Aftin.

Aftin Ross: Oh. Hi, this is Aftin. So, think it would be helpful to hear a little bit more about some of the challenges that are being experienced with regard to the IFUs. I'm not sure that at least I'm personally familiar with this and so we would certainly want to provide you with a thoughtful response. If you could perhaps reach out to the mailbox with a little bit more background with regard to this, we'll certainly look into that and get back to you.

Joan Melendez: Thank you.

CDR Kim Piermatteo: Great. Thank you, Aftin. And thank you Joan for your question. At this time, I think I'm going to circle back to some of our previously submitted questions that we would like to share.

So, the first question, Aftin, that I'd like to address to you is the question is, will there be more content similar to town hall three discussing review recommendations?

Aftin Ross: Yes, there will be. We have planned similar content for discussing some of the review submissions in future town halls. In fact, we encourage you to attend our next town hall where we will be discussing device modifications and how that may impact your submission.

CDR Kim Piermatteo: Thanks, Aftin. Alright, Chris I'm going to come to you with another previously submitted question as well. Chris, the question is, how does the revision to the 510(k) Sterility Guidance impact firms?

Christopher Dugard: Thank you. Yes, so the biggest change, of course, is what I discussed in that it's now considered a category A modality. And while this reduces the regulatory burden, for example, there's a lower amount of recommended information you need to submit in a 510(k), it does not change the existing requirements around cycle validation, quality systems, et cetera. So as far as what a firm will need to do internally, that is not changed. But what has changed is the information you'll need to submit to the agency to support that.

CDR Kim Piermatteo: Thanks, Chris. Alright so I'm not seeing any raised hands from our attendees. If you guys do have a question or a comment, please raise your hand and we will call on you. I'm going to continue to go through some of our other questions. These are for our presenters and panelists. So Shani, I'm going to come to you with another question. The question is, how do you send information through eSTAR?

Shani Haugen: Yeah. The most up to date information can be found on our eSTAR program website, and the resources slides in this presentation includes a link to our eSTAR program. You will start the process by downloading the proper eSTAR PDF template from the website. The PDF template is an interactive form that will guide you through the process of preparing a comprehensive medical device submission. There are directions at the end of the template that will provide you with instructions on how to submit.

CDR Kim Piermatteo: Thank you, Shani, that's very helpful. So another question, I'm going to direct that back to Chris. Chris, the question is, what happens if a firm provides more information than what you recommend?

Christopher Dugard: Yeah. So Shani covered this a little bit, but we will review the information that was provided. So we may ask for more information, for example, if we believe there's a potential impact on patient safety. So, a common scenario we see is that a 510(k) submission will state that all sterilization validation information is included; however, only a test for sterility is provided. And then that would raise concerns about the adequacy of the validation and may prompt additional questions. So, we urge you, again, to take the least burdensome approach and provide only the recommended information per our guidance, The Submission and Review of Sterility Information and Premarket Notification Submissions for Devices Labeled as Sterile. Thank you.

CDR Kim Piermatteo: Thanks, Chris. Alright, I'm going to call on our audience member, May. May, I have unmuted your line. Please unmute yourself and ask your question.

May Meng: Hello. I have a question regarding the shelf life validation that is related to the sterilization. If accelerated testing was submitted to the manufacturer needs to submit later the real time aging, like testing information. What's, and also what's the minimal time that needs to be tested in the shelf life validation? Thank you.

CDR Kim Piermatteo: Thank you, May. I'm going to turn this over to Shani to provide your response.

Shani Haugen: Great and thank you for that question. So in general, no. A subsequent 510(k) is not needed to provide the results of real-time shelf life information. Unless, of course, that is something, a device-specific issue that you have a review team. In general, the way that companies expand shelf life, or address additional shelf life testing, is referring to another guidance document titled "Deciding When to Submit a 510(k) for a Change to an Existing Device." That guidance document addresses similar kinds

of issues. So in general, if the same method or protocol described in the previously cleared 510(k) is used to extend the shelf life, then generally a new 510(k) is not needed. But when there are methods or protocols that are not described in a previously cleared 510(k) that are used to support shelf life claims, submission of a new 510(k) would likely be required. But we do encourage you to attend our next town hall where we discuss our modifications guidance that I just mentioned. And then I apologize, you had a second part to your question.

May Meng: Yeah. What's the minimum accelerated time span that needs to be submitted for the shelf life validation?

Shani Haugen: Thank you. So the amount of time that your accelerated aging should simulate should be consistent with your proposed shelf life. So, if you have a shelf life of 18 months then your accelerated aging should reflect that 18 month shelf life.

May Meng: Okay, thank you.

CDR Kim Piermatteo: Thank you May and thank you Shani for your response. Alright, at this time, I'm going to go back to Ryan. Ryan, I have a question for you. The question is, how do master files impact the sterility review?

Ryan Ortega: Yeah, thanks Kim. And for this response, I'll focus more on our traditional device master files rather than, say, our sterility master file pilots since this town hall is really covering our regular process for premarket review of sterility information. I'll briefly mention and plug that we do have the sterility master file pilot programs, which we discussed in our previous town halls and we're also going to discuss those again in some more granular detail in future town halls. This is really to help to differentiate between those two types of master files, the traditional device master files that have been around for a long time and the sterility master file pilots.

And so, for those traditional device master files, this type of submission really exists because sometimes device submissions, they may need to leverage data or other information. Like methodological information from another entity, like a contract sterilizer or a contract research organization. These master files, they may contain trade secrets or confidential commercial information or financial information from that other organization that that other organization might not necessarily want to share. And so that other organization, the contract research, or the sterilizer, they can submit a device master file to FDA that has relevant information about their process or their method so that the device manufacturers device admission can reference that master file, can reference that information from the other entity while still maintaining the confidentiality of the trade secret or the confidential commercial information. Usually, these traditional device master files are only reviewed when they're referenced in a device submission, and they're really considered in the context for that specific device. They're generally not reviewed on their own without being referenced. And we really just kind keep them in our files, in our internal tracking system, until they are needed when they're referenced in a submission.

CDR Kim Piermatteo: Thank you, Ryan. Alright, next I'm going to go to Chris. Chris, I have a question for you. The question is, if a sterilization method was not mentioned during the presentation, is it automatically a novel method?

Christopher Dugard: Thanks for that. No. Just because we did not discuss it here does not mean the modality in question is automatically considered a novel method. If you have a technology or a modality and are unsure of how it will be viewed by the agency, we encourage you to reach out to the relevant review division. And you can also consider submitting a pre submission or Q sub to discuss in more detail.

CDR Kim Piermatteo: Thanks, Chris. Again, if you have a question, please raise your hand in Zoom and we will call on you. I'm going to circle back to Shani for another question. The question is, how do you find out if your device has a specific ETO and ECH limit?

Shani Haugen: Thank you, Kim. So, ISO 10993 part 7 identifies some devices with specific EO and ECH residual limits, and it also addresses limits for devices used with pediatric populations. So, you can also search, in addition to that standard, can also search FDA's guidance database for device-specific FDA guidance documents. And you should also be familiarizing yourself with applicable special controls for your device type to understand any specific limits for your device type. I'd also encourage you to discuss your question with the appropriate FDA review group, or in a Q submission to understand if that particular device type does have concerns related to EO and ECH residuals.

CDR Kim Piermatteo: Thank you, Shani. Alright, the next question, I am going to direct that to Chris. I'm going to come back to you. The question I have for you is, can I utilize a non-recognized standard?

Christopher Dugard: Thanks. Yeah, good question. And the answer is yes. So all standards are voluntary. If you choose to use a non-recognized standard, however, we may request a gap analysis supporting that the chosen standard addresses the same concerns in a comparable manner. If the standard does not address all gaps, additional performance testing may be requested. Thanks.

CDR Kim Piermatteo: Thanks, Chris. Alright, so at this time, we do not see any more raised hands so I'm going to circle back to Ryan for one more question, Ryan, before we close out today. So that question that I have for you Ryan is, if we change sterilization modalities and no other change is made, is full biocompatibility testing needed?

Ryan Ortega: Sure. That's definitely one that we get from time to time, and it's a big question. And it can be fairly device specific, depending on the type of contact, what sort of change is being made, and the intended use for that device. That's why for questions about the biocompatibility impact, for changing sterilization modalities, we really strongly suggest contacting your review division, so the team that reviews that specific device, and ask them for input. And if it's several questions or if you would like a fairly technical answer, or perhaps even a chance to have some back and forth, that's where our Q-Submission Program really provides what we think is an effective way to get those questions asked and answered. So again, just another plug for our Q-Submission Program to ask questions like that.

CDR Kim Piermatteo: Great. Thanks, Ryan. And I thought we were going to move to close, but we do have another raised hand, which I think we have enough time for. So I'm going to call on Rudy. Rudy, I have unmuted your line. Please unmute yourself and ask your question or provide your comment.

Rudy: Thank you. For pyrogenicity testing, guidance or general practice is to conduct testing for the product by the lot. But depending on the manufacturing process yield or number of SKUs associated with my manufacturing process, the lot size in the traditional sense could be very small, like in the single

digits. So, if you look at the traditional aspect of a lot, the units going to pyrogenicity might be as many as the units that are intended to go to the patient. So, one way I've seen to work around this in the past is to define the lot in the term of pyrogenicity testing as those products that are going to sterilization cycle. So, all of that cycle is defined as one batch or one lot. Does the FDA accept this definition for lot in pyrogenicity testing or do they have any further guidance on how to determine lot size when building small lots?

CDR Kim Piermatteo: Thanks, Rudy. I'm going to turn it over to Shani to provide you a response.

Shani Haugen: Thank you for that question. There's going to be a lot of factors that are going to impact, and a justification for what a lot is or alternatives to lot testing. So for that question, I would recommend that you discuss your specific device and how you're defining a lot with your FDA review team who would be reviewing your device.

Rudy: Thank you.

CDR Kim Piermatteo: Thank you Rudy and thank you Shani. At this time, I'd like to make one last call out. If anyone has a question, please raise your hand at this time.

Seeing none. Thank you all again for your participation and your interaction during this segment of today's town hall. At this time, I want to turn it back over to Lisa to provide the final thoughts for today. Lisa.

Lisa Simone: Thanks Kim, and thanks again for joining us at today's town hall and sharing your questions and comments via email and the live QA. We had some great questions today related to shelf life validation, pyrogenicity testing, and we continue to see great interest in the IFU challenges and potential electronic labeling. We're looking forward to any information that you could share with us after the town hall, and also to seeing you at the next event. So, thanks for attending today, and now I'll turn it back over to Kim.

CDR Kim Piermatteo: Thanks Lisa for those final thoughts. As I mentioned earlier, printable slides of today's presentation is currently available on CDRH Learn at the link provided on this slide under the section titled Specialty Technical Topics and the subsection titled Sterility. A recording of today's town hall and a transcript will be posted to CDRH Learn under the same section and subsection in the next few weeks. This is also where you will find the recordings or presentations, transcripts and slides for previous town halls. And so a screenshot of where you can find these materials has been provided on this slide as well.

As mentioned earlier, and many of my other colleagues have mentioned, if you have additional questions or comments about today's topic or presentation or a future town hall, please submit them to medical device sterilization, all one word, at fda.hhs.gov (MedicalDeviceSterilization@fda.hhs.gov).

If you have any general questions about today's town hall, feel free to reach out to DICE at DICE@fda.hhs.gov. And lastly, as we mentioned before, we hope you are able to join us for our fourth medical device sterilization town hall which is scheduled on Thursday, February 29 from 1 to 2 PM Eastern time. You can find a listing of all of our upcoming town halls and other webinars via the link

provided at, well, sorry, at the link titled www.fda.gov/cdrhlearn and we look forward to hopefully you join us for one of those future ones.

So this concludes today's town hall. Thank you all again for joining us.

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