Medical Device Sterilization Town Hall: Sterilization Short Topics and Open Q&A
November 20, 2024

Moderator: CDR Kim Piermatteo

CDR Kim Piermatteo: Hello, everyone. Thanks for joining us for our fourteenth Medical Device Sterilization Town Hall. 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 with the FDA's Center for Devices and Radiological Health. I'll be serving as 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 multi-pronged approach, including regulatory flexibilities, supply chain analysis and mitigation, collaboration, innovation and communication, including this series of town halls.

For today's town hall, we'll begin with a segment of what we heard from you last time. Then our panelists will discuss recent sterility consensus standards recognitions and biocompatibility assessment considerations related to sterilization changes. Then we will have our live question and answer segment where we look forward to hearing from you. If you have a question or comment for our panelists today, please wait to raise your hand in Zoom until we transition to this specific part of today's town hall.

I'd now like to share a few administrative items before I introduce and turn it over to our panelists. First, please make sure you joined us through the Zoom app and not through a web browser to avoid technical issues. And second, 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 FDA's Office of Media Affairs at fdaoma@fda.hhs.gov.

I'd now like to introduce our presenters: Commander Scott Steffen, Senior Program Management Officer and EtO Incident Lead in the Division of All Hazards, Preparedness and Response within the Office of Readiness and Response within CDRH's Office of Strategic Partnerships and Technology Innovation or OST; Dr. Paulo Laranjeira, Biomedical Engineer in the Office of Health Technology Number four, for Surgical and Infection Control Devices within the Office of Product Evaluation and Quality, or OPEQ; Samuel Lum, Sterility Standards Advisor within the Division of Standards and Conformity Assessment in the Office of Readiness and Response within OST; Dr. Jianchao Zeng, Assistant Director for the Division of Standards and Conformity Assessment in the Office of Readiness and Response within OST as well.

Also joining us is Jen Goode, Biocompatibility Program Advisor on the Clinical and Scientific Policy Staff within CDRH's Office of Product Evaluation and Quality, or OPEQ; Dr. Jinny Liu, Polymer Chemist and Team Lead in the Office of Health Technology Number one, for Ophthalmic, Anesthesia, Respiratory, ENT, and Dental Devices in OPEQ; Dr. Apra Garg, Biologist and Senior Staff Fellow in the Office of Health Technology Number six, for Orthopedic Devices in OPEQ; and Dr. Dale Rimmer, Chemist and Senior Reviewer in the Office of Health Technology Number three, for Gastro, Renal, OB/GYN, General Hospital and Urology Devices in OPEQ as well.

Thank you all for joining us for our town hall today. At this time, I'll now turn it over to Scott to start us off. Scott…

CDR Scott Steffen: Yeah. Thank you, Kim. And thank you all for joining us for our fourteenth Sterilization Town Hall. Before we get started with our discussion today, we'd like to take the opportunity to discuss a question we received in our mailbox. Question, as manufacturers of a FDA approved tabletop vaporized hydrogen peroxide or VHP low temperature sterilizer, we encounter challenges when each instrument's IFU must be updated to specify our brand of VHP sterilizer. Given the FDA's recognition of VHP as a mainstream sterilization technology, would the FDA consider allowing the use of generic terminology such as quote, "autoclave" end quote, or quote, "VHP rated" end quote, instead of specifying the brand of the VHP sterilizer used. This change could significantly reduce the burden on manufacturers and facilitate easier adoption by sterile processing departments or SPDs enabling them to use FDA approved VHP systems like ours as alternatives or backups without additional hurdles.

Answer. Generally, tabletop sterilizers would not be used for terminal sterilization in medical device manufacturing, but rather in health care reprocessing. Typically, the topic of reprocessing is beyond the scope of our town halls. However, we felt that this is an important point to address. Vaporized hydrogen peroxide low temperature sterilizers from different manufacturers have different cycle configurations, which may impact how a specific medical device is sterilized.

While there is an FDA recognized consensus standard for the validation of VHP sterilization cycles, there is no consensus standard for VHP sterilizer equipment manufacturing. Specifically, there is a lack of consensus standards that cover minimum labeling, safety, performance and testing requirements for these types of low temperature sterilizers. Thus, it is necessary to submit premarket authorization of a medical device demonstrating that it can be safely and effectively sterilized using the intended vaporized hydrogen peroxide low temperature sterilizer.

We've shared this timeline previously in all of our town halls. Highlighted in the lower right corner is the existing link for some recently recognized standards that our team will discuss in this town hall.

In today's town hall on medical device sterilization, we're taking the opportunity to discuss two short topics with our sterilization experts related to sterility standards and biocompatibility. The short topics are shown here. These include topic one, the impact and recognition of recent sterilization-related standards and topic two, biocompatibility assessment considerations related to sterilization changes. Now, let me pass it to Paulo to get the discussion started on our first short topic.

Dr. Paulo Laranjeria: Thank you, Scott, and welcome, everyone. I'm going to start on introducing the impact and recognition of recent sterilization-related consensus standards. Previously, town hall five introduced you to the CDRH Standards Program. We discussed the value of using consensus standards, the benefits of seeking FDA recognized consensus standards in device submissions and announced the complete recognition of three key sterilization consensus standards in early 2024.

Given the importance of having new sterilization techniques, we are pleased to share with you three additional consensus standards FDA has decided to recognize during today during today's program.

So let's look first, why does CDRH strongly encourage the use of recognized consensus standards? As outlined in the FDA's guidance titled Appropriate Use of Voluntary Consensus Standards in Premarket Submission for Medical Devices, there are two suitable voluntary uses of consensus standards in the

premarket process. Use of a declaration of conformity, DOC, in accordance with section 514c1b of the FD&C Act in general use, which can be applied to any standard.

Recognition is FDA's formal identification of consensus standard, after determining that it is appropriate for manufacturers to declare conformance using the DOC to meet relevant requirements. Once FDA has decided to recognize a consensus standard, our online database will be updated to include such consensus standards, along with a recognition number and the supplemental information sheet, SIS, which will identify the extent of that intended recognition. When a manufacturer is citing a consensus standard and a declaration of conformity is included, a complete test report is not typically necessary.

Now, Jianchao, do you have anything else to add?

Dr. Jianchao Zeng: Thank you, Paulo. Yes, I actually do. The FDA encourages external and internal interested parties to recommend consensus standards for recognition. We may recognize all, part, or none of the consensus standard. We will publish the rationale for recognition in the FDA recognized consensus standards database.

FDA regularly updates decisions in the publicly available FDA recognized consensus standards database. We may withdraw for recognized consensus standards as appropriate generally to accommodate new versions and will list an appropriate transition date to the new standard in the recognized standards database.

Sam so can you tell us why CDRH strongly encourages the use of consensus standards?

Samual Lum: Alright, thank you, Jianchao. Well, first, strongly encourage FDA recognized consensus standards because they have FDA's confident that conformance will support device performance and processes when appropriately used. The content of consensus standards can provide clear regulatory expectations because there may be clear standardized test methods that eliminate the guesswork and how to do an assessment. There may also be a clear performance and acceptance criteria.

And as a result, these standards may potentially eliminate extraneous tests that would have been asked otherwise, saving both time and effort by leveling expectation. And then, as we are familiar with the consensus standards recognized, we tend to ask fewer additional information questions and the documentation when recognized standards are used together with the declaration of conformity during interactive review. And finally, CDRH knows that international consensus standards promote harmonization as they are relied upon by multiple jurisdictions, ultimately benefiting global health and trade.

Dr. Paulo Laranjeria: Thank you, Jianchao and Sam for your feedback. I would like to add that the type of information sponsors should submit and the FDA needs to review as supporting documentation to support a declaration of conformance will vary based on the specific consensus standards. For more information, we recommend that you refer to the appropriate use guidance referenced earlier. Now, I'll turn it over to Sam for the next discussion point.

Samuel Lum: Great. Thanks, Paulo. So now what consensus standards do we intend to recognize, and why did this happen between the regular spring and fall recognition cycle? And importantly, what was the process for the early recognition?

So we pointed out back in the spring, the FDA's Division of Standards Conformity Assessment is being very responsive to industry. Since town hall five, we made the decision of our intent to recognize three additional consensus standards related to sterilization. And today, we're describing those three updates.

Our intent to recognize two new consensus standards, along with one revised standard from partial to a complete consensus standard. Normally, the process for recognizing these standards takes place twice a year, in the spring and in the fall. If it's a significant consensus standard, however, we can consider it any time between those two as an off-cycle process by promoting techniques outlined in the standard.

Along with more to come in this fall, the FDA is proactively facilitating the adoption of alternative methods to ethylene oxide, sterilization, enhancing quality and advancing harmonization. Paulo will now discuss our first new standard.

Dr. Paulo Laranjeria: Thank you, Sam. So the first newly recognized consensus standard we will talk about today is ISO 11737, part 3, that was published in 2023. And the title is Sterilization of health care products, microbiological methods, part 3, bacterial endotoxin testing.

This consensus standard is important because testing for pyrogens is necessary for the release of many health care products where bacterial endotoxins are the predominant pyrogenic contaminant. We acknowledge that this consensus standard currently has overlapping requirements with FDA recognized AAMI ST72. Now, Sam, can you go over this recognition process of this standard?

Samuel Lum: Yeah, thanks, Paulo. I'm really excited to go over this slide. It's a case study of how we-- some insight into how CDRH actually recognized this 11737 part 3. So earlier in July, manufacturers requested this recognition to our internal email inbox. The FDA, through DSCA, our Division of Standards Conformity Assessment, acknowledged his request a day later on July 17.

We convened the sterility specialty task group and appointed panel of experts to formally review the standard and recommend a recognition, which they recommended a complete recognition. DSCA concurred and identified the consensus standard, along with its recognition number and the SIS and updated our publicly available recognized consensus standard database on September 9.

As a result, directly following this, sponsors may cite these consensus standards with a declaration of conformity as soon as the recognition decision appears in the database. And as a regular part of list 63, a Federal Register notice will formally announce these standards covered today along with additional recognition decision in the near future.

Dr. Paulo Laranjeria: Okay, now, on the second standard that we are going to talk about is ISO 11140 part one. That was published in 2014 and is a Sterilization of health care products, chemical indicators. This includes the general requirements for chemical indicators that demonstrate exposure to a sterilization process.

Recognition process and decision of this document was partially recognized by the FDA in August 2015. FDA reassessed this consensus standard to be aligned with our guidances for chemical and biological indicators and decided to change the partial recognition to a complete recognition as identified in our update to the database. This consensus standard specifies general requirements and test methods for

sterilization mutual variable process indicators and chemical integrators, including process indicators used for recently established sterilization method added to category A vaporized hydrogen peroxide or VHP. FDA decision to completely recognize this standard is important for the current sterilization situation because it enables the use of additional types of indicators that are compatible with modalities like vaporized hydrogen peroxide.

Finally, our third standard is ISO 13004. That was published in 2022. And it's also for the Sterilization of health products, radiation, substantiation of selected sterilization dose, method VDmaxSD. This standard aids sterilizers and manufacturers is substantiating a radiation sterilization dose to achieve an appropriate sterility assurance level of 10 to the minus 6 or less, as well as a method to audit the continued effectiveness of the dose.

Similar to our case example in 11737 part 3, we convened a team of experts to analyze the content of the standard. Sterility STG recommended a complete recognition, of recognition of ISO 13004 and DSCA formally agreed and updated our database in September 2024. FDA decision to completely recognize these standards is important for the current sterilization situation because radiation sterilization is an alternative sterilization method to ethylene oxide. And this standard extends the method of selection and substantiation of sterilization doses, increasing the applicability of the sterilization method. Sam, this is what I had to share for today.

Samuel Lum: Great. Thanks, Paulo. I'll now turn it over to Jianchao for our final discussion point.

Dr. Jianchao Zeng: Thank you, Sam. So how has CDRH been involved and how can interested parties get involved in standards development to advance new modalities? So sterilization standards work is very much a CDRH wide and a collaborative effort. So we have been involved in this area for quite some time and I've also initiated the new activities to help address the current challenges in maintaining a resilient supply of sterile medical devices.

Our long-standing activities supporting sterilization-related standards include 35 formal sterility liaisons and 12 additional sterility experts in CDRH who participate in 38 standards committees across multiple SDOs, such as AAMI, ASTM, IEST, and USP. To date, we have recognized over 140 sterilization standards.

As a result of the current sterilization challenges, our more recent activities include-- we recognized 24 sterilization related standards in the past 18 months alone, nine complete recognitions in 2024, and 15 complete recognitions in 2023. CDRH has been very involved in efforts to advance the development of consensus standards related to sterilization. Internally, CDRH created a task force to help inform and integrate our FDA liaisons and subject matter experts' involvement in standards development to support timely recognition and new initiatives.

The task force interfaces with CDRH's ethylene oxide tiger team among several other teams to ensure our cross-office standards activities are informed and harmonized across CDRH, to help meet our proactive goal to reduce reliance on ethylene oxide for sterilization of medical devices, supporting the adoption of new sterilization modalities.

So, Sam, can you share how everyone else can also get involved?

Samuel Lum: Yeah, definitely. So those of you listening here and your colleague, getting involved is something we definitely encourage participation in because we know that standard development can help support the novel sterilization modality. These standards that exist for specific modality may help to move the modality to, for example, a different category, as we've seen with vaporized hydrogen peroxide, the category A as per our 510(k) sterility guidance. And the broad participation by interested parties help to ensure that consensus is met for newer modality and incorporate everybody's needs.

To end our section, Jianchao can you talk about how consensus standard recognition are requested?

Dr. Jianchao Zeng: Thank you, Sam. So DSCA accepts recognition requests from both internal and external sources. Recognized consensus standards are a vital tool to promote quality and regulatory efficiencies. It is important to note that this many sterilization recognitions are possible because all of the parties that have participated in that development have collaborated to ensure that this consensus standards address specific regulatory needs.

So please reference the DSCA website for request contents and the recognition and withdrawal of voluntary consensus standards guidance document. You can send your requests and any questions or comments to the following email address, CDRHStandardsStaff@fda.hhs.gov.

Now, let's review some examples of recent recognized sterilization standards. So this slide includes sterilization consensus standards recognition from Federal Register notice lists, of list of 59 through list of 62 that covers the period time period of December 2022 through May 2024. Now, I'll pass it over to Jen to get the discussion started on our second short topic.

Jen Goode: Thank you so much, Jianchao. The short topics we intend to discuss in this session include some general considerations for how changes in sterilization may impact biocompatibility, some considerations related to specific types of sterilization processes and some considerations related to chemical and physical characteristics of a medical device.

So when changes are made to the sterilization modality of a medical device, there may be impacts on device performance. However, in this part of the town hall, we will focus only on potential impacts to biocompatibility. Apra, can you start us off by sharing some thoughts on this topic?

Dr. Apra Garg: Thank you, Jen. Biocompatibility assessment of the final finished device is recommended, which includes packaging and sterilization. In some cases, biocompatibility information can be leveraged from a device that was sterilized with a different method, example, ethylene oxide versus steam, or the same method using a different protocol. Example, change in radiation dose.

Jen Goode: Thanks, Apra. Jinny, from your perspective, what are some things you think are important to consider?

Dr. Jinny Liu: Thanks, Jen. Yeah, an understanding of the device materials, and properties is needed to understand the potential sterilization impact on biocompatibility. Material compatibility information and considerations for one type of sterilization method do not necessarily apply to a non-sterilization method. For example, a device that is compatible with gamma irradiation may not be compatible with hydrogen peroxide sterilization.

Jen Goode: Thank you, Jinny. Dale, are there any other general considerations you'd like to add?

Dr. Dale Rimmer: Yes, I want to point out that the AAMI technical information report 17, that is TIR17, provides helpful summary information regarding the compatibility of various materials with sterilization methods and may serve as a reference for understanding the potential compatibility of device materials with the chosen sterilization method. And manufacturers of specific sterilization equipment may also have a similar list of compatible materials for reference.

Jen Goode: Thanks, Dale. So now let's think about what are some method-specific considerations for how sterilization changes may impact biocompatibility. Apra, would you please start us off?

Dr. Apra Garg: Sure. There are many types of sterilization processes, including radiation, which includes Gamma, X-ray and E-beam, steam, ethylene oxide, hydrogen peroxide, liquid chemical and dry heat sterilization. When changing from one sterilization method to another or when changing the sterilization parameters for a particular sterilization method, the following could potentially impact device biocompatibility.

For steam sterilization, consider whether device materials are sensitive to changes in moisture level and cycle parameters such as temperature, exposure time, pressure and dry time. For dry heat sterilization, consider whether device materials are sensitive to changes in cycle parameters such as temperature and exposure time.

Jen Goode: Apra, thanks for helping us understand what to consider for steam and dry heat sterilization. Dale, what should we be thinking about for radiation sterilization processes?

Dr. Dale Rimmer: For radiation sterilization, including Gamma, X-ray and E-beam, we recommend considering whether device materials are sensitive to changes in cycle parameters such as radiation intensity and dose. When considering dose, changes to the packaging and changes to the layout configuration during sterilization can also impact dose. Metals and ceramics are generally compatible with most radiation sterilization methods. However, according to AAMI TIR17, if high dose rates result in localized, severely elevated temperatures at the surface of metals, this could change the material and therefore biocompatibility aspects.

Polymers may have different sensitivity to sterilization methods depending on radiation dose, type of polymer, device manufacturing and design, irradiation environment, and dose rate. That is dose delivered per unit of time. For example, according to AAMI TIR17, low dose rate radiation methods such as gamma radiation may be considered worst case compared to e-beam to evaluate biocompatibility. Use of inert gas or vacuum during packaging may help eliminate the effect of oxidation for radiation sterilization as described in AAMI TIR17. Antioxidants and radical scavengers can improve radiation resistance. But changes to these types of additives can also impact the biocompatibility of a medical device.

Jen Goode: Thanks, Dale. That's really helpful. Jinny, can you share with us how we should be thinking about hydrogen peroxide sterilization and ethylene oxide sterilization?

Dr. Jinny Liu: Of course, for hydrogen peroxide sterilization, it's important to consider whether device materials are sensitive to changes in chemical concentration and the cycle parameters, such as exposure

time. The sensitivity of the material may be dependent on the device material manufacturing process and the type of hydrogen peroxide used, whether it's gas versus plasma.

There are materials such as cellulose that are not compatible with hydrogen peroxide sterilization due to the strong oxidation capability of this sterilization method. While for ethylene oxide sterilization, it's important to consider whether the device materials are sensitive to changes in cycle parameters such as pressure, yield gas concentration, temperature, relative humidity, cycle duration and aeration time. This cycle parameters may not impact the biocompatibility of metals and ceramics.

However, for polymers, it's important to understand where the polymer's thermal transition temperatures fall as compared to their operating range of the EO sterilization method, which can be up to 65 degrees C. If there's a phase change near the sterilization operating temperature range, this can impact biocompatibility. Some polymers are also sensitive to moisture and this can also impact biocompatibility. In addition, for all device materials, it's important to understand whether changes to cycle parameters will result in change to the EO residues such that product specifications are no longer met.

Jen Goode: Thanks so much, Jinny. Switching gears slightly, I'm wondering if we can talk a little bit about how to think about packaging and sterilization changes. Apra, can you speak to this?

Dr. Apra Garg: From a biocompatibility assessment perspective, changes in packaging or changes in sterilization can affect what types and amounts of chemicals are transferred from the packaging to the medical device, as well as sterilization residuals.

Jen Goode: Thanks so much. So now we will discuss considerations related to chemical and physical characteristics of the medical device. Apra, can you start us off again by speaking to some chemical characteristics that can be impacted by sterilization changes. In particular, how should we be thinking about sterilant residual levels.

Dr. Apra Garg: Sure sterilization changes may impact the chemical characteristics of the medical device, including changes to chemicals that can be released from the device or that are-- or that are on the surface of the device. When considering whether sterilant residual levels are met for ethylene oxide, hydrogen peroxide and liquid chemical methods, acceptable ethylene oxide residual levels can be found in ISO 10993 part 7 or device specific standards and guidances. Acceptable hydrogen peroxide residual levels can be derived from the literature for specific devices and indications. Acceptable liquid chemical, like formaldehyde, glutaraldehyde residual levels have not been defined for all medical devices, but residuals can be compared to those of other devices used to treat the same indication.

Jen Goode: Thanks, Apra. So you did mention that there could be changes in the chemicals released from a medical device. I'm wondering, Dale, if you might want to share more on this aspect.

Dr. Dale Rimmer: Sure. When considering whether the type or amounts of chemicals released from the device can change, we recommend considering whether device materials could be sensitive to a particular sterilization method. This could impact the release of chemicals from inside the device components, for example, the bulk materials, and could impact release of chemicals from the device's surface. In addition to the release of chemicals, chemicals at the surface of the device could be modified with sterilization, and this could also impact biocompatibility.

Jen Goode: Thanks, Dale. So let's also discuss how sterilization changes may impact the physical characteristics of the medical device. Jinny, do you have any thoughts on this?

Dr. Jinny Liu: Yes, sterilization change can also impact the physical characteristics of the medical device, including surface properties, forces on surrounding tissue, for example, mechanical, thermal, electromagnetic, geometry and presence of particulates, among others. These changes may impact biocompatibility. For example, implantation and all thrombogenicity endpoints may be impacted by changes in device stiffness due to further cross-linking from UV, chemical or radiation sterilization process. Or they can be impacted by changes in surface roughness or geometry.

Jen Goode: Thanks, everyone. To close out this topic, I wanted to mention that we do have some online resources and guidance is available relevant to biocompatibility, which include an online biocompatibility assessment resource center, a guidance on the use of ISO 10993-1 for biocompatibility assessments, a guidance on biocompatibility testing of medical devices that can be conducted as part of the CDRH ASCA program, as well as the question and answer guidance on pyrogen and endotoxin testing. The links to these resources are included at the end of the presentation. I will now pass it back to Scott for a summary.

CDR Scott Steffen: Yeah. Thank you, Jen. And thank you, Paulo for all those great conversations and touch points that we've talked about.

The next slide includes the resources mentioned earlier in the presentation, along with the full URLs that you can access after the presentation. And really to summarize things, today, we had a robust discussion on the following topics. We discussed the impact and recognition of recent sterilization-related standards and shared CDRH's additional involvement and the value of industry engagement in standards development to further alternative sterilization modalities. We also discussed biocompatibility assessment considerations related to sterilization changes and described how changes to sterilization methods and packaging may impact biocompatibility.

Before we open the discussion, I am excited to announce our final town hall of our medical device sterilization town hall series, which will commence almost a year ago with our inaugural town hall on January 10, 2024. Please join us for this 15th town hall on December 4, 2024. We'll be sharing a short topic on research and modeling on the diffusion of vaporized hydrogen peroxide or VHP, through select polymeric materials.

We'll also have some other recent updates to share with you all, and we'll be discussing the content and impact of the overall town hall series and then close with some thoughts about next steps. We'll include the live Q&A on topics identified by the audience and topics provided prior to the event via our medicaldevicesterilization@fda.hhs.gov mailbox. Information about the town hall series can be found at the link here. So now let me turn it over to Kim to close us out.

CDR Kim Piermatteo: Thanks, Scott. And thank you, too, again, to all of our panelists for joining us today and providing a great discussion.

We will now transition to our question-and-answer segment of today's town hall. First, though, I would like to introduce Dr. Ryan Ortega, who will be joining our panelists for this segment. Ryan is a Regulatory

Advisor on the Regulatory Policy and Combination Products Staff within CDRH's Office of Product Evaluation and Quality. Thank you for joining us, Ryan.

Next, I'd like to go over how we will manage this segment and a few reminders. So 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 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.

When asking your question, please remember to limit yourself to asking one question only and try to keep it as short as possible. And we appreciate that you may have a very specific question involving your device or scenario. However, we might not be able to provide such a specific response to that question. Therefore, we will try to provide a broader response to your question.

After you ask your question or provide your comment, please lower your hand. And 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 your questions and comments today, I would like to start us off with a few questions to our panelists. And the first question, I would like to direct that to Jianchao. So Jianchao, the question is, how frequently does the Agency recognize standards?

Dr. Jianchao Zeng: Thank you, Kim. FDA typically updates the Recognized Consensus Standards Database and publishes their recognition list in the Federal Register notice twice a year. So occasionally, if there is a public health need, so FDA will recognize the standards more frequently, as we described in this town hall. But we note that this is not a common occurrence.

CDR Kim Piermatteo: Thanks, Jianchao. For the next question, I'm going to come to Jen. So, Jen, the question is, when a change is made to sterilization that can impact biocompatibility, do I need to redo all of my biocompatibility testing?

Jen Goode: Thanks, Kim. That's a great question. As noted in our published biocompatibility guidance, it may not be necessary to conduct testing for all or a portion of the biocompatibility endpoints suggested in the FDA matrix of this guidance. For example, if the sponsor is able to document the use of a particular material such as 316L stainless steel in a legally marketed predicate device or a legally marketed device with a comparable tissue exposure and is able to explain why the change in sterilization is not expected to adversely impact biocompatibility, additional biocompatibility testing may not be necessary to address some or all of the biocompatibility endpoints recommended for consideration in attachment A. If you would like to discuss a specific situation or if you have any questions about the suitability of your approach, we do encourage you to consider submitting a Q-Submission.

CDR Kim Piermatteo: Thanks, Jen. Okay, I have another question that we previously received that I'd like to hand that to Paulo. So, Paulo, the question is, what is a regulatory ready standard?

Dr. Paulo Laranjeira: That's a very good question, Kim. FDA considers a regulatory ready standard to be one that features clear test methods and acceptance criteria, which make it useful for conformity

assessment purposes. Not all standards lend themselves to this, but when they do, they are suitable for the declarations of conformity, the DOC, which typically reduces the amount of documentation needed in a device submission.

CDR Kim Piermatteo: Great. Thanks, Paulo. Again, I encourage our attendees to raise your hand if you have a question or comment for our panelists today. But Apra, I'd like to come to you with another question. Apra, the question is, how do biocompatibility assessments for material mediated pyrogens differ from sterility assessments for pyrogenicity of bacterial endotoxins?

Dr. Apra Garg: Thanks, Kim. So as noted in our published biocompatibility guidance, pyrogenicity information is used to help protect patients from the risk of febrile reaction. There are two sources of pyrogens that should be considered when addressing pyrogenicity. Material mediated pyrogens are chemicals that can leach from a medical device during device use and pyrogens from bacterial endotoxins can also produce a febrile reaction similar to that mediated by some materials.

Implants, due to their contact with the lymphatic system, as well as sterile devices having direct or indirect contact with the cardiovascular system, the lymphatic system or cerebrospinal fluid, regardless of duration of contact and devices labeled as non-pyrogenic, should meet pyrogen limit specifications. Bacterial pyrogens are traditionally addressed as part of the sterility assessment, as discussed during the sterilization town halls on February 27, 2024, and August 7, 2024.

If a sponsor would like to label their device non-pyrogenic, even if there are no endotoxin limit specifications based on the nature of body contact, we recommend that both bacterial endotoxins and material-mediated pyrogens be assessed. As noted in our published pyrogen and endotoxin testing guidance for devices and drug materials, firms should assess the risk of the presence of non-endotoxin pyrogens, such as material-mediated pyrogens, if the risk assessment indicates that non-endotoxin pyrogens may be present, it may be more appropriate to use the rabbit pyrogen test.

CDR Kim Piermatteo: Thanks, Apra. Okay, again, I encourage anyone on the call, if you have a question or comment for our panelists, please feel free to raise your hand in Zoom. But I'm going to circle back to Jinny. Jinny, I'm going to come to you with another question that we previously received. And Jinny, the question is, the biocompatibility guidance indicates that material-mediated pyrogenicity testing is not needed if chemical characterization of the device extract and previous information indicate that all patient contacting components have been adequately assessed for pyrogenicity. Can analytical chemistry testing or information on the materials of construction and manufacturing be used to address material pyrogenicity?

Dr. Jinny Liu: Thanks, Kim. That's a good question. If the medical device manufacturer can explain why the sterilization change is not expected to change the chemistry of the device, they may be able to leverage information from the prior sterilized device, where material-mediated pyrogenicity has been addressed to justify that new chemical, new material-mediated pyrogenicity testing is not needed. But if the sterilization change modifies the chemistry of the device, which can potentially release new chemicals that have not been assessed for the pyrogenicity or such information is not available from literature, then it's unlikely that the analytical chemistry data can be leveraged for this assessment.

CDR Kim Piermatteo: Thanks, Jinny. Okay, I'm going to come back to Dale. We're going to keep going through some previously submitted questions that we had until someone would like to raise their hand.

Dale, I'm going to direct this question to you. Dale, the question is I have a permanently contacting polymer device where everything is the same, except that I am now proposing to use a different sterilization method. Do I have to conduct exhaustive extractions for my analytical chemistry testing since the bulk materials are unchanged?

Dr. Dale Rimmer: Well, it may depend on your device's polymers, what sterilization method you are changing from and what sterilization method you are changing to. For example, if you have a polymer where radiation sterilization can impact the overall degree of cross-linking in the device and you change to ethylene oxide sterilization, you may have to think about whether less cross-linking could result in the release of more analytes from the bulk polymer. You also would have to think about whether the chemicals in the ethylene oxide process could be absorbed and/or interact with the chemicals in the bulk polymer such that released analytes could change or could increase over time.

CDR Kim Piermatteo: Thanks, Dale. Alright, I'm going to call on Roberta. Roberta, I have unmuted your line. Please unmute yourself and ask your question or provide your comment.

Roberta, I see that you have unmuted your phone. I don't know if you're double muted. We're still here trying to see if you can unmute your line. Roberta, I'm going to go ahead. I'm going to--

Roberta Bergeron: Is that. Is that better?

CDR Kim Piermatteo: That's good. There we go. Great, okay.

Roberta Bergeron: Sorry, it was-- I got a pop up that was not related to mute, and I got a little confused. Sorry about that. I just had a quick question about testing frequency for endotoxin for products. What is the recommended test frequency for that-- not material mediated, but for LAL endotoxin testing, the BET. Is their recommended frequency or just there's a lot of discussion around this in my company, and I kind of wanted to get the organization's input on that.

CDR Kim Piermatteo: Sure. Thanks, Roberta, for that question regarding testing frequency. I can turn it over to Apra first, and then if anyone else wants to join in, please feel free.

Dr. Apra Garg: Sure. So the sterility guidance has recommendations on the testing frequency for bacterial endotoxin. And basically, the sponsors should have an endotoxin monitoring plan. So FDA necessarily do not prescribe a particular plan. However, it does say that either do batch testing or if you have an alternate to batch testing, then you have to have a risk assessment on why that endotoxin monitoring plan may be every two months, three months, is acceptable based on the risk from the manufacturing process. And SD72 provides a lot of recommendations on how to conduct this risk assessment. So essentially batch testing, if not, then have a risk assessment plan for whatever monitoring plan you choose to have for bacterial endotoxins evaluation.

Roberta Bergeron: Thank you.

CDR Kim Piermatteo: Thank you, Roberta, for your question and thank you Apra for the response. Alright, again, please feel free to raise your hand in Zoom. I'm going to circle back to Sam. So, Sam, the question I have for you is, I see that FDA recognized consensus standards database has two recognized

standards for bacterial endotoxin testing ST72 and ISO 11737, part 3. Should I reference the most recent recognized standard or do I need to reference both?

Samuel Lum: Alright, thanks. And this might be helpful in the context of the previous asked question. But in essence, between the AAMI ST72 and the ISO 11737, part 3 standard, you may choose to reference either one because both of the scopes specify that the general criteria to be applied in the determination of bacterial endotoxin, the component, the raw material employing the test method, they all reference amebocyte lysate reagents. However, it's important to note that newly published standards may have different requirements from an older one, and therefore we recommend that you perform a gap assessment before choosing your reference standard in the submission.

CDR Kim Piermatteo: Thanks, Samuel. Alright I am going to circle back to Paulo. Paulo, another question that we received was, I have a new sterilization modality and I am developing a process indicator for it. However, this sterilant is not listed in the FDA chemical indicator guidance. How should I proceed?

Dr. Paulo Laranjeria: Thank you, Kim. Yes, that's a very good question related to chemical indicators. Yeah, the FDA recognized standard ISO 11140, part 1 would be helpful in this situation. While additional requirements for indicators intended for use with other sterilization methods are not specifically provided in the standard, the general requirements would apply and provide a basis for the indicator performance. So that's our recommendation that you look into ISO 11140, part 1.

CDR Kim Piermatteo: Thank you, Paulo. Alright, next up, I'm going to call on Lindsey. Lindsey, I've unmuted your line. Please unmute yourself and ask your question or provide your comment.

Lindsey E.: Hi. Can you hear me okay?

CDR Kim Piermatteo: Yes, we can.

Lindsey E.: Okay, great. Lindsey from Cook Medical. And with regards to a reduction in an EO gas concentration to achieve a more sustainable cycle, along with an increase in dwell time and changes to evacuation and aeration parameters, does-- sorry, does the FDA agree that this should not impact biocompatibility of devices?

CDR Kim Piermatteo: Thanks, Lindsey. I'm going to open it up to the panelists. I don't know if Jen, if you wanted to start and then anyone else can chime in. Or if you need further clarification, we can do that too.

Jen Goode: Well, this is Jen. I can start, but I think I'm going to then turn it over to Apra. I think that it may depend on what device materials you have. And so I don't think that we can globally say overall that those particular changes, reduction in EO gas concentration, increase in dwell time and then changes to the evacuation and aeration parameters would a priori always be okay. I think you might have to think about your device materials and of course, you just have to confirm that you still have the sterility you need. Apra, is there any clarification you wanted to provide on that?

Dr. Apra Garg: I think, as you noted, Jen, it will depend on the materials. So what I heard was maybe changes in parameters such as the exposure time and aeration time. Is that correct, Lindsey?

Lindsey E.: Yes.

Dr. Apra Garg: Yeah, so I believe we will have to think about the compatibility of the temperature of exposure to the material and maybe making sure that the residual levels-- I mean, of course, you will check that by part 7 that it is within acceptable range. So, I'm sorry, it's not a direct answer. It will depend on material. For some materials, you know like metals may be easier to assess than for polymers. And I would ask Dale or Jinny to add to what I said, if they have any additional comment.

Dr. Dale Rimmer: Thanks, Apra. This is Dale. I think that if the only change is a shorter exposure time for your ethylene oxide method, as long as there are no other impacts on performance, this could be used to support that no additional biocompatibility testing is needed. If you would like to discuss a specific situation or if you have any questions about the suitability of your approach, we encourage you to consider submitting a Q-Sub.

Lindsey E.: Okay. Thank you very much.

CDR Kim Piermatteo: Thanks, Lindsey. And thank you, Jen, Apra and Dale for providing some comments. Next, we have a question coming from Beluh. Beluh, I have unmuted your line. Please unmute yourself and ask your question or provide your comment.

Beluh Mabasa: Thank you very much for the time. I have one question, please. My question is ISO 14937 as the recognized consensus standard also by FDA until now. Hello?

CDR Kim Piermatteo: Yeah, Beluh, I hear you. Can you-- I didn't hear. I'm sure other people did. But can you just repeat that consensus standard. It's ISO 1437, is that what you said? I apologize.

Beluh Mabasa: Yeah, I want just to know if ISO 4937 as recognized consensus standard too.

CDR Kim Piermatteo: So is ISO 4937 a recognized consensus standard by FDA? Is that what you're asking?

Beluh Mabasa: That's correct. That's what I'm asking.

CDR Kim Piermatteo: Yeah. I don't know if Paulo, did you want to address the comment?

Dr. Paulo Laranjeria: Yes, Kim. I can address that. Yeah, that's a good question. Yes, if you go into our standards database, your recognized database, you're going to find that, that one is recognized also. So 4937, which is a guidance to validate different sterilization modalities that do not have a specific standard, it's recognized by the Agency too.

CDR Kim Piermatteo: Thanks, Paulo.

Beluh Mabasa: Yeah, thank you. Thank you very much, Paulo.

CDR Kim Piermatteo: Thanks, Beluh. Okay, I don't see any more hands raised, but I would like to come back to Jen. So again, I encourage anyone on the call to please raise your hand if you have a question or

a comment for our panelists today. But Jen, I wanted to come back to you with this question. And that question is, if testing for material-mediated pyrogenicity is needed, how is this testing conducted?

Jen Goode: Thanks, Kim. So when it's determined that material-mediated pyrogenicity testing is needed, we do recommend that the companies assess material-mediated pyrogenicity using traditional biocompatibility extraction methods such as 50 degrees C for 72 hours, 70 degrees C for 24 hours, or 121 degrees C for one hour per ISO 10993, part 12, which was published in 2021.

And then we also recommend that they use pyrogenicity testing such as outlined in the USP, the USP pyrogen test, which is a USP rabbit test or an equivalent validated method. For devices that contain heat labile or heat sensitive materials such as drugs, biomolecules or tissue derived components, which may have the potential to undergo deformation or material configuration or structural change at the high temperatures I previously cited, in these cases, extraction at 37 degrees C per ISO 10993-12 is recommended.

CDR Kim Piermatteo: Thanks, Jen. Alright, I'm going to go to Apra. Apra, I'd like to come to you with another question that we received. As hopefully our attendees, if they have a question, they can raise their hand in Zoom. But Apra, the question I have for you is, can we leverage a predicate that is from a different manufacturer but is sterilized using the same sterilization modality as the subject device to address the biocompatibility risk due to a change in sterilization modality?

Dr. Apra Garg: Thanks, Kim. That's a great question. So prior history of use for a reference predicate may be helpful if the bulk material of the subject device and the predicate device have the same material and composition. However, as discussed in the panel, you will also need to consider whether your manufacturing process, including packaging, could change the device chemistry, which could impact the need for additional biocompatibility information or testing.

CDR Kim Piermatteo: Thanks, Apra. Okay, I think, I don't see any more raised hands. But again, I encourage you to raise your hand if you have a question or comment for our panelists today. But before we close out or if no one has any questions, I'd like to come to Jianchao for one more question that we previously received. And Jianchao, that question is, although we highlighted three completely recognized standards in today's discussion, how should I use a partially recognized standard?

Dr. Jianchao Zeng: Thank you. This is a very good question. A partial recognition of a consensus standard means that some clauses of the standard cannot be recognized because they are not consistent with the CDRH's regulations, guidances, or another currently recognized standard. So such clauses are excluded from FDA recognition. So when using such a partially recognized consensus standard, the user should not use those conflicting clauses in their testing and assessment. Instead, the user should refer to the supplementary information sheet or SIS sheet in the FDA recognized consensus standards database for the rationale for partial recognition. If alternatives are used, the user should provide justifications for the validity of the alternatives. So those alternatives and their justifications should be submitted in supporting documentation. So that said, a manufacturer may include a declaration of conformity to the recognized elements of the standard.

CDR Kim Piermatteo: Thanks, Jianchao. Okay, I see no more raised hands. So I think at this time I will move to wrap up today's town hall. So thank you all for your participation. I will now turn it back over to Scott to provide his final thoughts for today. Scott.

CDR Scott Steffen: Yeah. Thank you, Kim. And thank you all again for joining today's town hall and for sharing your questions and comments via email and during the live Q&A. We appreciate those questions and the robust discussion today as it related to a couple items.

We discussed three recent off cycle recognitions, including some examples from the past couple of years. We discussed many aspects like sterilization modality changes, packaging, chemical and physical characterization regarding biocompatibility testing. We talked about testing frequency with bacterial endotoxin testing and the idea of having a monitoring plan. We also talked about the use of sustainable EtO cycles and how that could impact biocompatibility.

The question came up about ISO 14937 and if it was recognized. We confirmed it was recognized and referenced our standard database on seeing where standard-- what standards are recognized by FDA. We also talked about how material-mediated pyrogen testing is conducted. We also kind of rounded it out with the idea of leveraging predicates for biocompatibility testing and the use of partially recognized standards. Again, this was a really great and robust discussion and we thank the audience for the questions that they provided, and I'll just send it over back to you, Kim, to wrap us up and close us out today. Thank you.

CDR Kim Piermatteo: Thanks, Scott. So from my end, for my final thoughts as a reminder, printable slides of today's presentation are currently available on the Events page for this town hall and on CDRH Learn. A recording of today's town hall and a transcript will be posted to the Events page and CDRH Learn in the next few weeks and a screenshot of where you can find these materials on CDRH Learn has been provided on this slide.

If you have an additional comment or question about today's town hall as well as if you have a comment or question for a future town hall, please email medicaldevicesterilization@fda.hhs.gov.

Additionally, you can find a listing of all of our upcoming medical device sterilization town halls and other webinars on our CDRH events page at www.fda.gov/cdrhevents.

And lastly, as Scott mentioned I just want to provide another reminder that our next and final sterilization town hall will be held on Wednesday, December 4, from 2:00 to 3:30 PM Eastern Time. We hope you you're able to join us for that town hall as well.

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

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