Medical Device Sterilization Town Hall:
FDA's Modifications Guidances and the Use of Device Master Files in Reviews
February 29, 2024

Moderator: CDR Kim Piermatteo

CDR Kim Piermatteo: Hello everyone and welcome to our fourth town hall on the topic of medical device sterilization. Thank you 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'd like to share two administrative items regarding our web pages. 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 townhalls and a link to the printable slides for today's town hall. I encourage you to take note of this section in CDRH Learn because this is where we will also post the recordings and transcripts for these town halls. I'll also remind you about this at the end of today's town hall as well.

Second, we have retired our CDRH Webinars web page. Upcoming and past town halls, webinars, et cetera are now listed on the CDRH Events web page. I've included the full URL to the CDRH Events web page on a slide towards the end of today's presentation for you to reference.

Now on to some general administrative items for today. One, please make sure you've joined us through the Zoom app and not through a web browser to avoid technical issues. 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. And lastly, we look forward to interacting with you today. If you have a comment or question, please wait until we transition to this segment of today, which follows the presentations to raise your hand.

I now have the pleasure of introducing our presenters for today's town hall. Lieutenant Commander Scott Steffen, Senior Program Management Officer and EtO Incident Lead in the Division of All Hazards Preparedness & Response in the Office of Readiness and Response within the Office of Strategic Partnerships and Technology Innovation, or OST. Dr. Ryan Ortega, Regulatory Advisor on the Regulatory Policy and Combination Products Staff within the Office of Product Evaluation and Quality, or OPEQ. And Christopher Dugard, Assistant Director in the Office of Health Technology Number 4 for Surgical and Infection Control Devices in OPEQ as well.

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

LCDR Scott Steffen: Thank you for joining us for our fourth sterilization town hall. Before we get started with our discussion today, we'd like to take the opportunity to answer some questions we received in our mailbox after our last town hall on February 7th.

Question one. What guidance does the FDA have on the use of nitrogen dioxide as an alternative sterilization modality in lieu of ethylene oxide?

Answer. Our revised 510(k) sterility guidance, which was issued on January 8th, 2024, includes a description of the categorization scheme for sterilization methods of 510(k)s regarding established category A versus established category B or novel methods within a 510(k) submission; along with the appropriate information that firms should submit for those sterilization categories.

Regarding nitrogen dioxide, the information that might be needed in a 510(k) could be device specific or dependent on if we have previously reviewed the specific nitrogen dioxide cycle or a similar cycle. We recommend submitting a Q-Submission to your relevant review team to discuss the appropriate sterilization information to submit per our guidance.

As for performing validation studies, being there is not a specific standard to nitrogen dioxide, we recommend you consult ISO 14937:2009 on how to validate your process.

Question two. I represent a medical device manufacturer who is thinking of moving some of our devices from ethylene oxide sterilization to radiation. What references do I have to consider for if I need a new 510(k)?

Answer. Thank you for your question, which turns out to be very timely. The short answer is we have a guidance titled, Deciding When to Submit a 510(k) for a Change to an Existing Device. This guidance discusses the decision-making process. Luckily, this guidance is the topic of today's town hall, where our speakers will walk through the process. So please stand by as I introduce today's topic.

Question three. Is there any way for us to bundle the 510(k)s since they all will have the same sterilization information?

Answer. We want to make sure that we're applying the least burdensome principles and streamlining the premarket review experience for both manufacturers and the review team where possible. To that end, it may be appropriate to bundle submissions considering factors such as if the device is being bundled have similar indications, rely on similar data for the change, or are reviewed by the same review team. If you have questions about bundling of specific devices, you can reach out to your review team for input. We also recommend you consult our bundling guidance, Bundling Multiple Devices or Multiple Indications in a Single Submission, for more information.

We also had some additional questions related to master files that Dr. Ortega will address later, so please stay tuned.

Now on to today's topic. Next slide, please.

We've shared this timeline previously, which shows major milestones related to EtO since 2019. Today's topics relate to several items highlighted in yellow, like our master file pilots and the recent revision to the 510(k) Sterility Guidance on January of 2024. Next slide, please.

Today's town hall on medical device sterilization will focus on submission modifications and our master file pilots. Our learning objectives today are to understand FDA's expectations for submission modifications by leveraging our When to Submit a 510(k) for a Change to an Existing Device; hereafter, called our Mods guidance, or our Modifications to Devices Subject to Premarket Approval (PMA) guidance, and to understand the use of device master files for sterility review, what it means to use master files, the difference between traditional master files and sterility master file pilots, and the different master file pilot programs that we have. Next slide, please.

Now, I'll pass it over to Chris Dugard, who will walk us through our modification guidances.

Christopher Dugard: Thank you, Scott. My name is Chris Dugard. And today, I'll be discussing FDA's expectations for modifications to devices and our submission expectations. Next slide, please.

These are the two guidances relevant to this discussion today, Deciding When to Submit a 510(k) for a Change to an Existing Device, Guidance for Industry and Food and Drug Administration Staff, and Guidance for Industry and Staff Modification to Devices Subject to Premarket Approvals-- The PMA Supplement Decision Making Process. These guidances provide assistance when determining if a change to a device will need a new 510(k) for devices subject to that review pathway or which supplement is appropriate for changes to PMA devices. Internally, we refer to these as the Mods guidances, so, if you ever hear that term being thrown around, these are the guidances we're referring to. Next slide, please.

So, the majority of my section will be going over the 510(k) modifications guidance. This guidance aids manufacturers who intend to modify a 510(k) cleared device or other device subject to 510(k) requirements in deciding whether a change exceeds 21 CFR 807.81(a)(3) and as a result, needs a new 510(k). This regulation states a new submission is needed if the device is one that the person currently has in commercial distribution or is reintroducing into commercial distribution, but that is about to be significantly changed or modified in design components, method of manufacture, or intended use.

The following constitutes significant changes or modifications that require a Premarket Notification. One, a change or modification in the device that could significantly affect the safety or effectiveness of the device. For example, a significant change or modification in design material, chemical composition, energy source, or manufacturing process. Or two, a major change or modification in the intended use of the device. Any device making those types of changes will need to be reviewed by the agency through 510(k). This does not include devices that are 510(k) exempt or require a PMA. This is also limited to medical devices and not other FDA regulated products. Next slide, please.

So, this guidance was created with these guiding principles in mind. And we recommend that you also keep them in mind when you're using this guidance. The first is changes made with intent to significantly affect safety and effectiveness of the device. This is set apart from changes that could impact safety and effectiveness but are not necessarily intended to. For changes where the goal is to affect the safety and/or effectiveness of the device, a new submission is likely needed, and you can end your assessment there. If your change is not intended to affect device safety and effectiveness, then an initial risk-based assessment should be done to determine, whether it can, either positively or negatively. Note the

nuance here is that we expect the assessment to include safety and effectiveness, which is different from other types of risk analysis that focus primarily on device harm. For this reason, the term risk-based assessment is used.

You should also consider the unintended consequences of the change. For example, changing a sterilization modality does not have a potential impact on the sterile specification. It could also impact device materials that affect biocompatibility. This type of potential effect on biocompatibility would result in the need for a new submission. You should utilize risk management using the recommendations outlined in ISO 14971, Application of Risk Management to Medical Devices. Appropriate testing should be done to determine if a change could significantly affect safety and effectiveness.

If you determine a change does not need a submission, this should be backed up with appropriate verification and validation activities. Not needing a new submission does not mean you will not need to do any additional testing.

Evaluation of simultaneous changes. Each change should be considered individually, but also in aggregate to ensure one change will not have an effect on the other change. Excuse me. The change should be considered against the original device. If a preamendments device exists compare it to that. If a De Novo exists, compare the change to that device. If the cumulative changes or effects trigger the regulatory threshold for submission, a new 510(k) is likely needed. As noted, supporting a change does not impact safety and effectiveness means a new 510(k) may not be needed; however, internal documentation still needs to be done per your quality system.

If multiple changes are made, but not all of them trigger the need for a 510(k), all changes should still be described in the 510(k), so that the agency has a complete understanding of the modified device. Finally, please keep in mind that an SE determination is not guaranteed when you submit for your change. Next slide, please.

So, this guidance includes a number of flowcharts to aid you in your change determination. There are different ones depending on the type of change. This is the main flow chart that will guide you to the other flow charts. Is it a change where the intent is to improve the safety and/or effectiveness of the device? No, flowchart is necessary, you will likely need a new 510(k).

Is it a labeling change? Go to chart A.

Is it a technology engineering or performance change? Go to chart B, or D in the case of in vitro diagnostics.

Materials change, chart C, again, or D if it's an IVD.

This guidance does not address manufacturing changes; however, the impact those changes, those types of changes have on the above aspects should be assessed and should be determined if a new 510(k) is needed. Any change that is not necessarily encompassed by the above flow charts should use the risk-based assessment recommendations outlined in section E of the guidance. Next slide, please.

First, I will go through the labeling changes flowchart. The flowchart itself is rather busy, so instead of putting a picture of it up here, I thought I'd include the highlights. I will also provide an example,

but the guidance itself has quite a few examples for each change, so I do highly recommend reading the guidance for some additional information. Essentially, these are the labeling concerns that may result in the need for a new submission. Since the flowchart is quite easy to follow, I'll not go through each decision point. But I'm happy to answer questions at the end. Note that yes to these will likely result in the need for a new 510(k). These changes all may impact the way the device is used, which may have an effect on safety and effectiveness.

Since these town halls are focused on sterilization, I did want to provide some relevant examples. Please note that while I tried to find relevant examples of each situation, FDA's decision of whether 510(k) will be needed will depend on the facts of each individual situation.

One example would be removal of a modality for a device that was cleared with multiple modalities. So, let's say the device was cleared to be terminally sterilized with both steam and ethylene oxide. Seeing the push to reduce ethylene oxide use, you decide not to use that modality. And you want to remove it from the labeling. Is it a change to the indications for use statement? No.

Does it change, add, or delete a contraindication? No.

Is it a change to the warnings or precautions? No.

Could it affect the directions for use? Since this is terminally sterilized, it won't impact how the device is used, therefore, documentation is likely appropriate.

So, I also want to go over an example of a labeling change regarding sterility that will trigger the need for a new submission. So, let's say you have a reusable device with reprocessing instructions and end users are instructed to sterilize with steam, to add more flexibility, the sponsor would like to add VHP, vaporized hydrogen peroxide as an option for the end user. Testing for performance aside, does the labeling change trigger the need for a new 510(k)? Let's go through the flowchart.

Is it a change in the indications for use statement? No.

Does it add or delete a contraindication? No.

Is it a change in the warnings or precautions? No.

Could it affect the direction for use? Yes.

Is it a change from a device labeled as single use to reusable? No.

Is it a change from prescription to over-the-counter? No.

Is there a change to the device name or to improve readability or clarity? No.

Does the change describe a new disease, condition, or patient population? No.

Does a risk-based assessment identify any new risks or significantly modify existing risks? Yes, there could be compatibility and performance issues that need to be mitigated with additional testing since

you've labeled for a heat-based method and want to add a chemical-based method. That leads us to likely needing a new 510(k). Next slide, please.

So next I'll be discussing technology engineering and performance changes. Here are the highlights from flowchart B, which address these changes. Again, I will not go through each point, but will provide examples. One part of this flowchart I wanted to highlight is B.3.1. Generally moving from a category A modality to B or novel will require a new submission going from A to another A modality or from B to A should be evaluated under question B.3.2, which asks if the change can impact performance or biocompatibility.

So, I want to provide two examples regarding changes to sterilization. The first is an example of a change that will likely not require a new submission. Let's say you have a device that is terminally sterilized via steam, you want to tweak the critical parameters, but are otherwise not changing the validation method SAL and you're still adhering to the appropriate standard.

Is this a control mechanism, operating principle, or energy type change? No.

Is it a change in sterilization, cleaning, or disinfection? Yes.

Is it a change to a category B or novel method? Does it lower SAL, or does it change how the device is provided? No.

Could the change significantly affect performance or biocompatibility? Since this is the same modality, no other changes are being made, and an appropriate verification validation study was done and documented as appropriate, documentation is likely adequate.

The next example is a subtle twist on this change. You have a device that is terminally sterilized via steam. You want to switch to vaporized hydrogen peroxide.

Is this a change to a control mechanism operating principle or energy type change? No.

Is it a change in sterilization, cleaning, or disinfection? Yes.

Is it a change to a category B or novel method, lower the SAL, or change how the device is provided?

Now, the answer here would be no if you just looking at the flowchart. But if you go into the discussion below the flowchart and the guidance, you will see a bit more analysis is needed for this one.

I mentioned above if you are going from A to another A modality, you should proceed to question B.3.2, which asks, could the change significantly affect performance or biocompatibility? Going from a heat-based method to a chemical-based method does have the potential to impact biocompatibility and/or performance, so a new submission will likely be needed. Next slide, please.

So now we'll discuss material changes. Here are the flowchart highlights. But in the interest of time, I will not be going over any examples. This is also because it's simple to come up with sterility-related material changes since sterilization is considered a manufacturing process. I will also note that while

material changes often have implications in biocompatibility, that is not the focus of this talk, so, I respectfully ask that you avoid any questions specific to biocompatibility.

One thing to note that is related to sterility, a material change does mean you will need to evaluate the impact of the currently chosen modality has on the new material. So, the guidance has a number of very useful examples for all the discussed change types, so I encourage you to check that out. Next slide, please.

And finally, I want to discuss changes to PMA devices. Generally, the considerations are very similar to those done for 510(k)s. The difference is in the type of supplement that will be needed as a result of the change. If a submission is needed, you will either need a new PMA, panel track supplement, 180-day supplement, real-time supplement, or a 30-day notice. Since the focus of these town halls is sterilization, I will note that changes to a sterilization cycle that would normally result in not needing 510(k), if that was the appropriate pathway for the device, are appropriate for a 30-day notice if the device is a PMA device.

Changes that do impact biocompatibility or performance likely need a 180-day supplement. That said, if you have an accepted PMA master file as part one of our master file pilots, this may impact the type of submission needed for a particular change.

In fact, I will take this opportunity to wrap up my section and pass it to Dr. Ryan Ortega to discuss these master files. Thank you.

Ryan Ortega: Yeah, thank you, Chris. Appreciate the handoff. Next slide, please.

And so, hello, everyone. The next topic is an overview of the use of master files and sterility review and our related pilot programs. We've gotten a lot of interest in the pilots. But we're also hearing that some firms maybe aren't sure how to submit a master file and would like some clarity on the process. So, in this learning objective, I'm going to talk a little bit about how the sterility master file pilot programs might be able to facilitate making sterility changes to cleared or approved devices and I'll also talk a little about the potential value to those firms who are considering participation. Another key point is to distinguish between the sterility master file pilots and traditional device master files, which are regularly used in submissions like PMAs and investigational device exemptions. Next slide.

So, our sterility reality master file pilots are distinct from traditional device master files. Generally, the traditional device master files don't receive review outside of the context of a specific submission. They're not limited to specific subject areas, and they generally can't be used to reduce the need for a new device submission or supplement. On the other hand, sterility master files in these pilots, they are reviewed when they're received and this is to ensure things like consistency with the pilot notices, resolve any questions about the technical or administrative information, and ensure that we understand the scope of the devices that are potentially included in that master file. And you can submit a master file for the pilots in the same way you would submit really any other regulatory submission. You can submit an eCopy formatted master file through the CDRH portal, or you can mail a copy to the CDRH Document Control Center. You can find additional instructions and links for both options in our device master file web page and a link to that web page is in our resources slide.

Before I go into some of the specific pilots, I do want to stress that generally for these pilots, the submitter of a sterility master file can be a contract sterilization provider. Or it could also be a device manufacturer that conducts their own sterilization. And these pilots are helping us explore some creative ways that we can reduce the regulatory burden for sterilization changes while also helping to protect the sterile device supply chain. And also, we want to be sure that this still gives us assurance that sterilization cycles have been appropriately validated and an adequate sterility assurance level can be achieved in a repeatable controllable fashion. Next slide.

So, the ethylene oxide master file pilot was the first pilot that was announced and that was back in 2019 after the advisory committee meeting that we held that year in November. It's a direct result of some of the committee discussion and feedback from that meeting and some of the initial lessons learned from when we started the innovation challenge to reduce ethylene oxide emission. This pilot allows a participating sterilizer to submit a master file describing a sterilization change to an ethylene oxide cycle for PMA-approved devices.

So, this could be things like a reduction in ethylene oxide concentration or maybe a site change. And it can also include devices or device types that they propose to be within the scope of the master file they submit. Then that sterilization change that's in the master file can be made to those devices that are in scope in a post approval report as an annual reportable change instead of a PMA supplement. And so, what this means for a device manufacturer is that a sterility reality change that used to require a PMA supplement could be included in an annual report instead within this pilot.

And one thing to mention here is that there are some exclusions for this and some of our other pilots, for example, sterilization of devices for reprocessing, combination products are out of scope, devices regulated by CBER, or devices with alternative sterility assurance levels. I also want to note that the pilots are not mechanisms for a manufacturer to change things like device design, specifications, performance, or materials.

In order to understand the process in the submitted master file and for us to understand which devices could be in scope, we've asked for some technical information in the master file like a description of the sterilization process and validation information. We ask for some information about product definition for the process, some risk analysis, information, et cetera. This gives us a sense of what's being proposed in the master file. It helps us to ensure that the proposal is consistent with what we put in the pilot notice in the Federal Register. And this is generally how we set up our first pilot, but you can see that there are similar procedures outlined in the notices for the subsequent pilots too. Next slide, please.

So again, a PMA holder with a device that is in scope of a master file, and again, that master file can be from their contract sterilizer or their own master file if they do their own sterilization. That manufacturer can make the change described in the master file and they would report it in their PMA annual report instead of submitting a PMA supplement. The sterility master file pilots are, again, open to contract sterilizers who sterilize other manufacturers devices and to manufacturers who do their own sterilization. The master file holder who, so the entity that submits it, is expected to provide a six-month report for their master file to include any changes and any devices that have been added. For all of the pilots, these six-month reports also give us a mechanism for the master file holders to propose modifications to the master file, things like adding additional cycles or expanding the product definition that's described in the master file. We intentionally designed these pilots to be flexible and expandable when that's appropriate. Next slide, please.

The radiation master file pilot was actually our third pilot. It was released in April 2023, but I want to discuss it now because it's similar to the ethylene oxide master file pilot. Like that pilot, the radiation pilot targets PMA approved devices. It generally has the same inclusions and exclusions. So, this particular pilot supports changes from one gamma site to another, a change from gamma to another radiation source like X-ray or electron beam, a change for a reduction in the gamma radiation dose, or even a change from ethylene oxide to X-ray or e-beam.

This pilot has some similar processes to the ethylene oxide pilot, and it also leverages some lessons learned from the ethylene oxide pilot and also our outreach to sterilization providers. Similar to the ethylene oxide pilot, what this pilot means is that for a manufacturer with a device that's in scope of an accepted master file, a sterility change, like I just outlined, could be an annual reportable change instead of being submitted in a PMA supplement.

Like the other pilots, the scope of devices that fit in a master file in the pilot goes back to that product definition that we recommend to be included in the master file. So, you can see why that's a really important aspect of a proposed master file for each pilot. One aspect of this pilot that I'd like to point out, again, is that it can support changes from ethylene oxide to X-ray or e-beam. If you take a look at the pilot notice, you'll see that in this case, we ask for some information aimed at ensuring that this change modality isn't negatively impacting device performance or specifications. We also ask some things about how biocompatibility and material compatibility are being assessed to support that change. Next slide.

So, as I mentioned, the value that we're hoping to create here is similar to the ethylene oxide pilot. And it all goes back to the feedback that we received from the advisory committee about giving regulatory incentives and flexibilities where we can. The changes described in the radiation master file included in this pilot become annual reportable, rather than PMA supplement changes for devices that are in scope. Like the ethylene oxide pilot, we also expect a six-month report for a master file on the pilot. And we expect this to include any proposed changes to the process and any specific devices that have been added. And again, these reports can be a useful mechanism to expand the scope of your master file. Next slide.

So, the 510(k) pilot was actually the second one that we established in May 2022. But it's a little different from the other two, so I'd like to discuss it last. It has similar goals to the others, really, to pilot a creative way of using master files for sterilization processes in order to reduce the regulatory burden for sterilization changes also while still ensuring that devices are safely and effectively sterilized. This pilot focuses on exploring ways to support the use of sterilization modalities that could be alternatives to rigid chamber ethylene oxide sterilization. Specifically, this pilot supports changes from ethylene oxide, which is an established category A method per our 510(k) and sterility guidance to modalities that we would consider established category B or novel.

I just want to give you a quick reminder that some of the content from our previous town halls covered, what makes a method established category A, establish category B and novel according to our 510(k) Sterility Guidance, so, if you haven't heard that town hall, I definitely recommend going back and checking those out. And usually, a new 510(k) would be needed to make this kind of sterilization change, as Chris outlined. However, under this pilot, manufacturers of devices that are in scope of a master file in the pilot may choose to reference the master file and all of their sterilization validation activities in

their internal documentation to support a justification of not submitting a new 510(k) for the sterility change described in the master file.

Much of the technical information that we'd like to see in a proposed master file for this pilot is similar to the other pilots. There may be some variation in the type and amount of information that would be needed. And this is considering that many of the methods that may be eligible for this pilot don't have modality specific validation standards and may not have a well-established most resistant organism for biological validation. This is outlined in further detail in the Federal Register notice for the pilot. Next slide.

Similar to the others, we expect six-month updates for a master file in this pilot to include any proposed changes to the process and any devices that have been added. Again, this is important because this gives us an opportunity to track devices that are undergoing these changes since we aren't seeing new 510(k) submissions for them. Also importantly, the 510(k) holder wouldn't need to send in a submission or an amendment for the change. Rather, what they would do is include all of the information, including the justification for not submitting a new 510(k) and their reference to the accepted master file in their own internal documentation. One thing I really want to note that's important is that none of these pilots are waiving removing or replacing other statutory and regulatory requirements like our quality systems regulations, medical device reporting, or record keeping requirements. Next slide.

So, if you've tuned in to our town halls before, you may have seen our resources slide before. These next three slides include some of the resources that we mentioned earlier in the presentation, along with the full URLs that you can access after the presentation. Next slide, please.

So just to give a brief summary of what we talked about, we described FDA expectations for submission modifications in both the 510(k) and PMA space. We described how to use our When to Submit a New 510(k) Guidance, or our Mods guidance, as well as our PMA Supplements and Amendments guidance. We compared differences between the traditional device master files and a master file pilot. And we described the three master file pilots and how they might impact device review, particularly sterilization changes. Next slide.

So, our next town hall is scheduled for March 21st at 12 to 1:00 PM Eastern time. The proposed topics include the value of consensus standards, the use of standards in premarket review, and the FDA standards program in general. Now I will turn it back over to Kim to take us into the Q&A.

CDR Kim Piermatteo: Thanks, Ryan. And thank you, Scott and Chris for your presentations today. As Ryan mentioned, we'll now transition to our interactive comments and question and answer segment.

Joining our presenters today for this segment, we do have Dr. Suzanne Schwartz, Director of the Office of Strategic Partnerships and Technology Innovation, or OST. Dr. Aftin Ross, Deputy Director of the Office of Readiness and Response within OST. And Dr. Shani Haugen, Assistant Director in the Office of Health Technology Number Three for Gastrorenal, OB/GYN, General Hospital, and Urology Devices in OPEQ. Thank you all for joining our panel today.

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, please identify yourself and your organization, and then ask your question or provide your comment. If you have a question, please remember to limit yourself to asking one question only. And try to keep it as short as possible. After you ask your question or provide your comment, please lower your hand in Zoom. And if you have another question or comment, please raise your hand again to get back into the queue and I'll 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 presenters and panelists for a few questions.

Suzanne, the first question I have, I'd like to direct to you. The question is, how many town halls are you planning to hold?

Suzanne Schwartz: Thank you, Kim, for that question. Our initial plan for this town hall series was to start off with five, five town halls. And that we would be focusing on current sterilization challenges, what our past and present activities are, as well as to provide a baseline of information that's related to current premarket review needs and the challenges that are faced. The audience, everybody who has participated, has provided feedback as the town halls have progressed and in truth, we're learning a lot more about other topics that folks would like us to explore. So, we do anticipate adding additional topics and we want to encourage folks to continue sharing feedback and suggestions with us. If you feel that these town halls are helpful and you'd like us to extend the series, please, please, please let us know by using our medical device sterilization mailbox at medicaldevicesterilization, all one word, @fda.Hhs.gov (medicaldevicesterilization@fda.hhs.gov). Back to you, Kim.

CDR Kim Piermatteo: Thank you, Suzanne. Alright, our next question, I'll be directing that to Shani. Shani, the question is, you discussed EtO residuals as one device consideration for sterility review in the last town hall. If a process was modified lowering the EtO residuals, would that warrant a 510(k)?

Shani Haugen: Thank you, Kim. Well, to answer that question, the short answer is it will depend on what that new sterilization process is. So, the 510(k) modifications guidance document that we discussed today, Deciding When to Submit a 510(k) for a Change to an Existing Device, provides a lot of helpful information on this topic. If the sterilization process changes from one established category A method to another established category A method, so for example, if a traditional EO sterilization cycle was modified to have different cycle parameters, but it's still a traditional EO sterilization cycle, that generally would not need a new 510(k), if the change does not significantly affect the performance or biocompatibility of the device or constitute a major change or modification in the intended use of the device. However, if the sterilization process changes from a traditional EO sterilization cycle, which is an established category A method, to EO in a flexible chamber, which is an established category B method, then that type of change likely would need a new 510(k) submission, unless the sterilization provider is accepted into the 510(k) ethylene oxide sterility change master file pilot program, which Dr. Ortega discussed earlier in this presentation. Thank you.

CDR Kim Piermatteo: Thank you, Shani. Alright, our next question I want to ask, I want to direct that to Ryan. Ryan, the question is, if our company submits a master file to one of the pilots, do we have to already have specific cleared or approved devices included in the initial master file submission?

Ryan Ortega: Yeah. Thanks, Kim. This has been a fairly common question from different groups who are interested in the pilots. I will say that there does need to be some sort of a product definition provided

in the initial master file that gives us a sense of the scope, but this doesn't necessarily have to include specific devices. We really do need to be able to review the information about cycle design and validation within the context of ensuring that it makes sense for the product definition. So, we need some initial information related to things like device geometries, materials, what those devices' intended uses might be. But this could potentially be satisfied by proposing device types, for example, or a subset of a device type as the initial product definition.

In other cases, a master file submitter may want to list the specific devices to initialize the master file. If you are putting in a master file with some idea of those specific devices, that can definitely be helpful. But ultimately, we understand that there are pros and cons to validating cycles with specific devices versus representative devices for product families or even process challenged devices. We really want to be flexible and to work to support different approaches for developing the processes that we are receiving in stability master file submissions.

Additionally, these pilots are set up to support expansion of an accepted master file. So, the product definition could be expanded once the initial master file is in the pilot. What you start with doesn't have to be carried on throughout the entire process, it can be added to. We also ask that as specific devices are added to a specific master file, that those devices are indicated in the regular six-month report. Again, this helps us to keep our understanding of how the master files are being used and also track sterilization changes to clear the approved devices. Thanks, Kim.

CDR Kim Piermatteo: Thanks, Ryan. OK, at this time, we will now hear from our first live audience member. I am calling on Ferdous. Ferdous, I have unmuted your line. Please unmute yourself and ask your comment or ask your question or provide your comment.

Ferdous Al-Faruque: I appreciate it. Thank you so much. So, I was at a meeting recently where FDA officials said that predetermined change protocols may be suitable when trying to change sterilization methods and practices in the future. Could you talk about what your thoughts are on that? And if companies are interested in doing so, how would they go about talking to the FDA about it? And also, have you had instances where companies have come to you and said, hey, we'd like to use the PCCP process to try to get sterilization changes in the future? Thank you.

CDR Kim Piermatteo: Thank you, Ferdous for that question. I would like to turn it over to Ryan. Would you like to start providing a response or anyone else on our panel?

Ryan Ortega: Yeah. Thanks, Kim. I can start with this one. No. I think with respect to how the PCCP process has been developed, sterility changes would be in scope. So, there are opportunities, I think, to explore this as an option for facilitating some of these changes or even proactively thinking about how changes might be made in the future in device submissions. I would think that the best way to explore that option would be to maybe do a Pre-Sub with the review division. I think some of the considerations might be device specific. So, I think that would be maybe the recommended path forward if a device manufacturer was interested in utilizing a PCCP for that sort of a change.

CDR Kim Piermatteo: Thanks, Ryan. And thank you, Ferdous, for your question and comment. Alright, our next question is coming from Byron. Byron, I have unmuted your line. Please unmute yourself and ask your question or provide your comment.

Byron Lambert: Thanks. Byron Lambert from Abbott. I might have been at the same meeting as Ferdous because the PCCP, the Predetermined Change Control Plans, were discussed at the AAMI neXus meeting that FDA co-sponsors. My first comment is that just continue to be so appreciative of the FDA aggressively trying to work with the industry to figure out how to move toward sustainable sterilization. And this is just such a huge nut to crack to change the sterilization modalities and so, your ongoing communication of your commitment to helping industry do that in a safe and effective way is just so appreciated. And specifically on the master file programs, thank you for this town hall on it and for discussions. Again, a huge cadre of FDA people at the AAMI neXus meeting and just continuing, this has been very helpful to continue to figure out, we have a very complex supply chain across multiple independent divisions. So, figuring out how to navigate this is challenging. And you're continuing to work with the industry is very helpful and that PCCP concept is maybe a complement to master files is really interesting. So that's just my comment of appreciation.

CDR Kim Piermatteo: Thank you very much, Byron, for those comments. We greatly appreciate that. Our next, we don't have any other raised hands. So, if you have a question at this time, please consider raising your hand and asking your question or providing your comment to our presenters and panelists.

At this time, I'm going to circle back to Ryan for a question to ask that we previously received. Ryan, the question is, if we have a sterility master file in a pilot and want to expand it, for example, expand product definition, add, or change cycles, do we need a new master file?

Ryan Ortega: Yes. Good question. The questions about expanding master files in particular, product definition, as I've touched on previously, we definitely get some good questions about that. And as I mentioned previously, these pilots are set up intentionally to support expansion of an accepted master file. And there's a few ways that this can happen. So, one, if a sterilizer, maybe they have a master file of the pilots, they want to make a change like expanding the product definition that would be in scope, or maybe they want to change a psycho parameter target or ranges of parameters, even potentially adding new cycles. This can be proposed in one of those regular six-month reports under the pilot or also potentially in a standalone supplement to a master file, that's another mechanism to get that information added to a master file.

In both cases, the proposed revisions or the additions to a master file will be reviewed, like the original master file, to make sure that we have the information that we need to understand what's being proposed. We want to ensure that it's still consistent with the master file pilot outlined in the Federal Register notice and that any specific devices or device types that are intended to be a part of the product definition really make sense, given the technical and scientific information provided and what we have in our review records.

CDR Kim Piermatteo: Thank you, Ryan. Alright, I'm going to circle back to, actually, I'm going to call on our next stakeholder, 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 want to know more about what did you mean with the material change. Can you describe more, please?

CDR Kim Piermatteo: Thanks, Beluh. So just to clarify, you have a question about a material change?

Beluh Mabasa: Yeah. That's correct.

CDR Kim Piermatteo: OK. Thanks for clarifying. So, looking at Chris or Ryan, would you like to provide a response? Or I think Shani, you mentioned this as well.

Christopher Dugard: Hi. This is Chris. I'm sorry. Could you clarify the question one more time? Could you repeat that for me, please?

Beluh Mabasa: I want to know what did you mean by the material change? Can you tell me more, please?

Christopher Dugard: Yes. Certainly. Yeah, sorry about that. Yeah, so all we meant by material changes is a change to any raw component or material that's used to construct the device. For example, if you've got polyethylene and then you switch to some other polymer, you have to consider if that change is going to impact biocompatibility or performance of the device.

Beluh Mabasa: OK. It must be, include, all must be a medical grade, something like that.

Christopher Dugard: I'm sorry. Could you repeat that, please?

Beluh Mabasa: Medical grade, must be, I mean, if the medical device or the [INAUDIBLE] medical is not medically [INAUDIBLE], it can be also the scope of the medical change, I mean.

Christopher Dugard: Well, I do appreciate the question. Materials generally do have to be medical grade. However, if it's alright, biocompatibility questions and material change questions specifically are a little bit out of scope of this town hall. So, if you have questions related to that, I highly recommend you reach out to the appropriate review team.

Beluh Mabasa: OK. Thank you very much for your answer. Thank you.

CDR Kim Piermatteo: Thank you, Beluh, for your question. And thank you, Chris, for your response. Alright, our next question is coming from Jennifer. Jennifer, I have unmuted your line, please unmute yourself and ask your question or provide your comment.

Jennifer Daudelin: Hi. Thank you. Jennifer Daudelin with Proforma. I have a question about multiple changes. So, if, for instance, you have a clear device for a category A sterilization and you're moving to another category A sterilization, flowchart B says you don't need a 510(k). But if you're also going to change your packaging as part of that sterilization change and you go through flowchart B and it takes you to documentation, can we view those two changes individually and document both, or do we have to look at it cumulatively? And if it's cumulative, would that trigger a new 510(k)?

CDR Kim Piermatteo: Thanks, Jennifer. Go ahead, Chris. Sorry.

Christopher Dugard: Sorry about that. I jumped in early. Yeah, so I can take that one. Generally, both changes should be considered individually, but also in aggregate. So individually, if one change on its own might prompt the need for a new 510(k), generally, that's where you're going to have to go. And then you will need to discuss all of the changes in the 510(k) just so we have a complete understanding

of the device. But if you feel neither change results in a 510(k) on their own, but then considering an aggregate, the change might impact biocompatibility or performance, then yes, potentially, we may need a new 510(k). But ultimately, it really depends on the changes being made. But yes, you should consider the change both independently as well as in aggregate.

Jennifer Daudelin: Thank you.

CDR Kim Piermatteo: Thank you, Jennifer. And thank you, Chris. Our next question is coming from Lucie. Lucie, I have unmuted your line, please unmute yourself and ask your question or provide your comment.

Lucie Solon: Sure. Thank you. Can you please clarify when the master file should be submitted to the FDA? Because to me, it's not quite clear at what stage of the process is it with a new 510(k) submission or when the change is identified. And I'd like to ask the same question for the PCCP as well, if you could clarify what stage of the change process this should be submitted to the FDA.

Ryan Ortega: Yeah, sure. Great questions. This is Ryan. So, for the master file pilots, the master file in this case would be for a specific sterilization process. So, it doesn't necessarily have to be tied to a specific change for a specific device. We are essentially accepting these sterility master files for the pilots whenever an interested entity would like to submit them. And so, let's say a master file is submitted, it's accepted into one of the pilots, then for a device manufacturer with a device in scope of that accepted master file, for the two PMA ones, these would be PMA approved devices for the 510(k) pilot would be a 510(k) clear devices. These devices in some form or version are already cleared or approved, so they would potentially reference their master file to make a change after the approval or clearance. On the other hand, a, my understanding of the PCCP is that that is generally trying to be proactive about saying, if we have this predetermined change, here's how we would do it. So that would come in earlier in the process.

Lucie Solon: Thank you.

CDR Kim Piermatteo: Thank you Ryan. And thank you, Lucie.

Lucie Solon: Yeah. Thanks.

CDR Kim Piermatteo: At this time, I'd like to make one final callout. If anyone has a question or comment that they would like to provide, please raise your hand at this time. Alright, I'm going to call on Gerald. Gerald, I've unmuted your line, please unmute yourself and ask your question.

Gerald McDonnell: Hi, there. This is Gerry McDonnell from Johnson & Johnson. I just wanted to ask a clarity question on the scope of the master file pilot program. I know there's a lot of emphasis on a single sterilization provider, but with the scope of the master file program say that the same sterilization cycle could be performed at multiple providers, or multiple sites, or even multiple countries.

Ryan Ortega: That's an interesting idea, Gerry. These are pilots in the truest sense, right. We try to put down the notices, some procedures that we thought would help us to get to the endpoint of facilitating these changes. But it's still an experiment, we think a well-informed experiment, but we are open to ideas of what could potentially be added or could other types of changes be really helpful for us to

facilitate and how can we make that work out. Just because something isn't directly captured maybe in one of the pilot notices, we'd still maybe like to talk about it. Maybe it's something that could be implemented, or potentially implemented in some future activity. So, if that is something that is of interest, then we would encourage you or other folks to reach out to talk to us about your ideas.

Gerald McDonnell: Many thanks. And thanks for the innovation opportunities. We appreciate it.

Ryan Ortega: Thank you.

CDR Kim Piermatteo: Thank you, Gerry. And thank you, Ryan. We have time for one more quick question or comment. I'm going to call on a number. That number is 615212. I have unmuted your line, please unmute yourself and ask your question or provide your comment.

615212: I would like to ask you to share again the link to pull the presentation, please.

CDR Kim Piermatteo: Yes. Yes. We will be providing that on the next slide and that is a good segue to wrap us up today. So, thank you very much. Alright, so, like I said, at this time, we're going to move to wrap up today's town hall. On this slide, you will find some additional information. But before we go through all that, I'm going to turn it back over to Scott to provide today's final thoughts. Scott?

LCDR Scott Steffen: Yeah. Thank you, Kim. And thank you again for joining us for today's town hall and sharing your questions and your comments via email and during this really fruitful live Q&A. We're really glad to hear that you are finding these town halls to be very helpful and especially regarding the robust discussion on master files. We continue to listen to what you all would benefit from hearing about and are always looking at ways to integrate this feedback into our current and forthcoming town halls.

And I just want to reiterate that we had a great discussion along with great questions today regarding on a couple touch points like how the decision making process for when you submit a 510(k), what to submit for changes to PMAs and IVDs and how to determine what type of PMA supplement to submit, multiple changes that could be implemented into the same submission, EtO residual considerations, our master file pilots, how master files are processed, how many town halls that we're planning to have and what the future is holding for us, and then also touching on PCCPs and how to potentially implement them through the agency. This has been a really robust discussion. I know I've learned a lot personally and I hope everyone else has learned a lot.

And again, just thank you all for attending. And now I'll turn it back over to Kim to close us out. Thank you, Kim.

CDR Kim Piermatteo: Thank you, Scott. And thank you, everyone, for your participation today. As I mentioned earlier and, on this slide, printable slides of today's presentations are currently available on CDRH Learn. That is the first link that is provided on this slide. And it's 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 this same section and subsection in the next few weeks. And a screenshot of where you can find these materials has been provided on this slide as well.

Also mentioned earlier, if you have additional questions or comments about today's topic or presentation as well as if you have a comment or question for a future townhall, please email medicaldevicesterilization@fda.hhs.gov.

If you have general questions about today's town hall, feel free to reach out to us in DICE at DICE@fda.hhs.gov.

And you can find a listing of all of our upcoming town halls and other CDRH events via the link provided on the bottom of this slide. This is the one that I had mentioned earlier that this is where all of our upcoming events will be on the CDRH Events page. So, reference that URL.

And then lastly, we hope you're able to join us for our next Medical Device Sterilization Town Hall, which is scheduled, as Ryan mentioned, on Thursday, March 21st from Noon to 1:00 PM Eastern time.

This concludes our town hall today. Thank you all again. And have a nice day.

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