**Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process" - Final Guidance**
**October 12, 2023**

**Moderator: CDR Kim Piermatteo**

**CDR Kim Piermatteo:** Hello, everyone. Thanks for joining us, and welcome to today's CDRH webinar. 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 and CDRH's Office of Communication and Education. I'll be your moderator for today's webinar.

Our topic today is the final guidance titled, "Use of International Standard ISO 10993-1, Biological Evaluation of Medical Devices, Part 1: Evaluation and Testing within a Risk Management Process." This guidance was issued on September 8, 2023.

The final guidance reflects the FDA's current thinking about the type of biocompatibility information that should be provided in a medical device premarket submission for certain devices in contact with intact skin. The guidance was revised to add recommendations that were described in the draft guidance titled, "Select Updates for Biocompatibility of Certain Devices in Contact with Intact Skin."

We are holding this webinar to, one, provide an overview of the new Attachment G, which describes a new policy for certain devices that contact intact skin; two, explain related changes made to the electronic submission template and resource, or eSTAR, form; and three, answer questions you might have about this final guidance.

Before we begin, I'd like to provide two quick reminders for today's webinar. First, please make sure you've joined us through the Zoom app and not through a web browser to avoid any technical issues. And second, the intended audience for this webinar is industry. Members of media are encouraged to consult with FDA's Office of Media Affairs for any questions they might have.

I now have the pleasure of introducing our presenter for today's webinar, Jennifer Goode, Biocompatibility Program Advisor on the Clinical and Scientific Policy Staff within the Immediate Office of the Office of Product Evaluation and Quality, or OPEQ, in CDRH. We'll begin with a presentation from Jen and then field your questions about our topic. Thank you all again for joining us. I'll now turn it over to Jen to start today's presentation.

**Jennifer Goode:** Thank you. Today, I will be sharing with you how the biocompatibility guidance has been modified to address a new policy for biocompatibility assessment of certain devices in contact with intact skin. This new policy is described in Attachment G of the guidance, which was published on September 8, 2023.

In our webinar today, I will describe in more detail the purpose of this update to the FDA biocompatibility guidance. I'll describe devices, components, and materials, included in, and excluded from, the Attachment G update. I'll describe information and labeling needed for a premarket submission if a manufacturer decides to use the Attachment G recommendations to support a regulatory submission. I'll describe the changes made to the eSTAR form related to the Attachment G recommendations. And I'll describe some additional revisions made in the guidance, such as revisions needed to be consistent with the current recognized versions of relevant consensus standards.

So, let's start with why this particular change was made to the FDA biocompatibility guidance.

For certain medical devices or components contacting intact skin, many are made from synthetic polymers and natural fabrics that pose a very low biocompatibility risk. This is based on long history of safe use in legally marketed medical devices here in the U.S.

Attachment G describes a least burdensome approach for these devices that recommends specific material information to be included in a premarket submission in lieu of biocompatibility testing or detailed rationales. This approach supports the principles of the three R's, to replace, reduce, and/or refine animal use in testing, when feasible.

So, what are the included devices, components, and materials in the new Attachment G policy for certain devices in contact with intact skin? Let's look at them.

Section A of Attachment G explains that the described approach can be used if a medical device meets all of the bulleted items on this slide. First, the device or component can contact intact skin surfaces only. The 2018 revision of ISO 10993-1 describes intact skin contacting devices in clause 5.2.2, item a. It is important to note that this ISO category for intact skin contacting devices does not include devices in contact with mucosal membranes or open or healing wounds. Secondly, the approach can be applied regardless of the duration of use of the intact skin-contacting device. Lastly, the approach can be applied to intact skin-contacting devices made from one or more materials in the list in section B of this attachment. This material list is described in our next few slides.

Section B of Attachment G describes the specific materials for which this approach can be used. I won't go through all of these chemical names but would like to point out that if an intact skin-contacting device or component is made from one or more of these synthetic polymers, the Attachment G policy can be used.

On this slide, you will see more synthetic polymers that didn't fit on the prior slide but are listed in section B of our guidance. In addition, we've listed some natural fabrics that are also included in the Attachment G policy for certain medical devices contacting intact skin. For those abbreviations not spelled out on these two slides, I encourage you to refer to the guidance document itself, where all the materials are listed on PDF page 59.

We thought it would be helpful to describe some medical devices where this Attachment G approach could be used. In this first example, we are talking about biomicroscopes. These devices are used in the ophthalmologist's office for microscopic assessment of the patient's eye. For these devices, the headrest and chin rest contact intact skin, so the Attachment G approach could be used for these components.

Oximeters are another example of a medical device with intact skin-contacting components. These are small devices that slide over a patient's fingertip to measure blood oxygen levels. The intact skin-contacting components where the Attachment G approach can be used include the finger cushion, the external case, and buttons and sensors on the outside and inside of the case where there is skin contact.

Blood pressure cuffs are another example of a medical device where the Attachment G approach can be used. These devices include an inflatable sleeve that is wrapped around the patient's arm so that blood

pressure can be measured. Sometimes there is a pump that the clinician will use to inflate the cuff. So usually, all components of the device can be considered as contacting intact skin.

Our last example is an inflatable tube massager. These devices use air compression to help relieve minor muscle aches and pains, and they also increase circulation to the legs. For these devices, the components that wrap around the leg can contact intact skin. So, the Attachment G approach could be used.

In section A of Attachment G, we also identify several situations where we recommend discussion with FDA to determine if the Attachment G approach can be used. The guidance notes that if the new submission is planned for a device legally marketed in the U.S., and the marketed device was found to be toxic in previous testing, that prior to submission, a discussion with FDA using our Q-Submission process is recommended.

Similarly, if U.S. legally marketed devices result in adverse clinical findings that may be related to cytotoxicity, irritation, or sensitization, a Q-Submission is recommended prior to the new submission if use of this Attachment G approach is desired.

In addition, we recommend Q-Submission discussions if you want to use the Attachment G approach for intact skin-contacting devices indicated for use with neonates or pregnant women. We also recommend Q-Submission discussions for intact skin-contacting device-led combination products or intact skin-contacting devices comprised of biologically derived material, such as tissues derived from animal or plant material.

It is also important to understand what devices, components, and materials are excluded from the Attachment G approach.

Section C of Attachment G describes the types of materials that are excluded from this approach and provides the reason for exclusion. If your device or component falls into any one of these categories, the traditional biocompatibility approach would be used.

So, let's talk about the exclusions. First, this approach does not apply to components fabricated from materials that are not explicitly included in the Section B list that we just discussed. So novel materials and bulk metals, such as titanium, stainless steel, nickel, nitinol, gold, cobalt, chrome, and other metals are excluded from this approach. This is because these materials may introduce toxicity risks.

Next, intact skin-contacting devices that are stored in or contain fluids or creams are excluded because there is an increased risk that leachables can be transferred into the fluid or cream and then absorbed through the skin.

In addition, devices fabricated from in-situ polymerizing materials, absorbable materials, or hydrogels are not included in this Attachment G approach. This is due to the increased risk that polymerization or degradation products can change over time. For these materials, manufacturing processes can also impact the type and quantity of intermediate and final chemicals, which could introduce a toxicity risk.

Also excluded from the Attachment G approach are devices that contact breach or compromised surfaces, such as open wound or healing wounds. This is due to the increased risk that leachables can be transferred through breach or compromised skin.

Reprocessed single-use devices are also excluded because reprocessing chemicals can cause adverse biological responses, such as irritation. Finally, adhesives used to attach a device directly to the skin, such as electrode pads and on-body pump attachment systems, are excluded, as they also can cause adverse biological responses, such as irritation.

Attachment G also includes recommendations on what biocompatibility information and labeling to include with a premarket submission if this approach is used.

Section D of Attachment G lists the information needed for all types of premarket submissions. FDA is requesting a list of the materials used to fabricate the device with identification of those components and materials with only direct or indirect intact skin contact. In addition, we are requesting a statement confirming that the device materials are listed in Section B and have a documented history of safe use in legally marketed medical devices in contact with intact skin, such as through medical device reporting analysis and literature searches. We also are requesting a statement confirming that none of the exclusions listed in Section C apply.

If you are submitting an IDE application and would like to use the Attachment G approach, we also are asking that IDE progress reports include a discussion of any adverse biological responses seen with the IDE device intact skin components, including redness, swelling, irritation, sensitization, allergy or other immune responses, or reactions at the skin-contacting sites. In addition, we'd like to understand if the reactions have been attributed to a specific component of the device.

For marketing submissions, we are also requesting a statement that the manufacturer has documented in their Device Master Record how they have determined that the biocompatibility risks for their device are addressed, such that biocompatibility testing and a detailed rationale regarding manufacturing is not necessary to include in a premarket submission.

An example of a statement that would support this request is listed here and also provided in the guidance on PDF page 62. For example, the submission could include a statement indicating that the sponsor has documented in the Device Master Record that they have addressed any concerns that have been identified through biocompatibility testing, that is, cytotoxicity, irritation, and sensitization, or identified through manufacturing information based on the type of materials or formulation, if available, and the nature of contact, and/or relevant quality system requirements and post-market controls related to purchasing controls, production and process controls, acceptance activities, corrective and preventative actions, complaint files, and MDR reporting.

In addition, the guidance includes recommendations for labeling if the device is intended for use in a patient population that may not have the ability to identify adverse biological reactions related to cytotoxicity, irritation, or sensitization, such as patients with epilepsy or dementia or the vision impaired. In these cases, we recommend that manufacturers inform caretakers in labeling with a precaution discussing common adverse skin reactions. An example statement is provided here and also can be found on PDF page 63 of the guidance.

With this guidance update, we have also made some changes to the eSTAR form, which I will discuss now.

A new field has been added to the eSTAR form, where you are asked if the listed components are in contact with intact skin only and if all of the component materials are included in Section B of Attachment G in the FDA biocompatibility guidance.

If you answer yes to this question, a yellow field indicates that you should click on the Help Text, indicated by the blue question mark next to the question, for information on what to attach to your submission.

In the Help text is a summary of what to include in your submission. With your list of materials, we ask that you verify that the materials are on the included list and none of the exclusions apply. We also request a statement that you have addressed biocompatibility in your Device Master Record using the recommended example statement we just discussed. In addition, if a labeling statement is needed, we include the example statement here as well. Finally, there is a link to the FDA biocompatibility guidance for your reference.

I also wanted to review with you some additional revisions to the guidance.

We made some revisions elsewhere in the biocompatibility guidance, so throughout the guidance, to clarify text and to ensure consistency within the guidance, as well as with currently recognized versions of consensus standards. What you will notice is that some of the links in the footnotes are now referencing updated standards and guidances. We also added some language in the main body of the guidance on the ASCA program.

In addition, we included some updated language about studies not in compliance with the FDA Good Laboratory Practice Regulations. We did this to be consistent with the guidance issued earlier this year about general considerations for animal studies intended to evaluate medical devices. Finally, Attachment A of our guidance was updated to be consistent with the recommendations in ISO 10993-1 2018, Annex A, Table A1.

In conjunction with the publication of this updated guidance, our Biocompatibility Resource Center was also updated to be consistent with the changes to the guidance. So, you may want to bookmark that for a quick reference.

I hope that the information shared today has helped you to understand how we are considering certain devices in contact with intact skin. We think that the new Attachment G approach will be helpful for medical devices or components contacting intact skin and fabricated from certain synthetic polymers and natural fabrics, which pose a very low biocompatibility risk. These materials have a long history of safe use in legally marketed devices in the US for this indication.

We think that this new approach will provide a least burdensome option that leverages specific material information, manufacturing, and labeling statements that can be submitted instead of biocompatibility testing or detailed rationales. The eSTAR form has been updated to include this Attachment G approach. In addition, there are several minor revisions that we discussed today throughout the rest of the

biocompatibility guidance that we also hope will facilitate preparation of the biocompatibility information you provide to us with your submissions.

My colleagues and I want to thank you for your participation in this webinar. We are happy to answer any questions you have about the material that was presented today.

**CDR Kim Piermatteo:** Thank you, Jen, for that presentation. At this time, we will now transition to the interactive question-and-answer segment of today's webinar, where you get to ask your questions to our panel.

Joining Jen today on our panel is Dr. Simona Bancos, Biologist in the Division of Health Technology 1A for ophthalmic devices in the Office of Health Technology Number 1 within OPEQ; Dr. Molly Ghosh, Pharmacologist in the Division of Health Technology 5B for neuromodulation and rehabilitation devices in the Office of Health Technology Number 5 in OPEQ; and Dr. Jinny Liu, Lead Chemist in the Division of Health Technology 1A for ophthalmic devices in the Office of Health Technology Number 1 in OPEQ as well. Thank you all for joining our panel today.

Before we begin, I'd like to go over how we will manage today's segment and a few reminders. So, to ask a question, 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 and then ask your question.

When asking your question, please remember to limit yourself to asking one question only and try to keep it as short as possible. As well as we appreciate that you may have a very specific question involving your device or specific scenario; however, we might not be able to answer such specific questions; therefore, we'll try to frame a broader response based on what's proposed in the guidance.

And our panel is available to help you today to help you better understand and get clarity on what we intend in the final guidance, so we ask you to try to frame your questions with that in mind. After you ask your question, please lower your hand. If you do have another question, 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, I'd like to welcome our newest panelists with some questions we have gotten over the past weeks about this guidance. And so, for our first question, I'll be directing that to Simona. Simona, the question is, you indicated that we should submit a Q-Submission to discuss whether the new policy for devices with intact skin applies to devices indicated for use with pregnant women or neonates. Can you clarify what type of information should be provided in a Q-Submission for these types of devices?

**Simona Bancos:** Good afternoon. My name is Simona Bancos, and I am a biologist and biocompatibility focal point in OHT1, which includes division of ophthalmic, anesthesia, respiratory, ENT, and dental devices. Thank you very much for your question.

As summarized on slide 16 of the presentation and discussed in Section A of Attachment G of FDA's 2023 biocompatibility guidance, we recommend that companies submit a Q-Submission if their intact skin-contacting device is used in neonates and pregnant women, and they would like to apply the Attachment G approach. We recommend that in a Q-Submission, the company provides the approach

used to determine that the biocompatibility risk had been addressed for the subject population. This may include, but may not be limited to, the following, device description, including identification of device components that contact intact skin; confirmation that the device meets the Attachment G inclusion criteria and does not meet the exclusion criteria provided in Table G1; description of the materials that were used to manufacture the skin-contacting component or components of the device, including the chemical name, trade name, vendor, and safety data sheet, if available; if applicable, information on the company's prior experience with the device and device materials; whether they are aware of any adverse clinical findings reported for intact skin-contacting medical devices manufactured of the same type of material or materials; and information on why from an anatomical perspective the requested patient population will not be more at risk.

I hope that this information addresses the question received. Thank you.

**CDR Kim Piermatteo:** Thank you, Simona. Alright, our next question, I'll be directing that to Molly. Molly, the question is, you state that for all premarket submissions, all materials, including the color additives used to fabricate the device or component with direct or indirect skin contact should be listed. Could FDA provide guidance on what specific information about the color additives should be provided in the submission?

**Molly Ghosh:** Hi, this is Molly Ghosh. Good afternoon, everyone. I am the biocompatibility subject matter expert and biocompatibility focal point for OHT5. And thank you for the question, this is a great question.

So, the guidance has a link to CDRH information on color additives, see footnote 86 on page 61 of the guidance. In the CDRH Learn module at the bottom of this link, there is a description of the type of the color additive information that we recommend. For example, listing the name of the color additive should be sufficient for intact skin-contacting devices with up to 30 days of contact.

For intact skin-contacting devices with long-term contact, meaning greater than 30 days of contact, we recommend that additional information, such as chemical name, purity information, amount present in the device, et cetera, and a toxicological risk assessment for the color additive explaining why the color additive present in your device will not pose any safety risks for their intended use we provided in the submission.

Hope this helps to answer the question. Thank you.

**CDR Kim Piermatteo:** Thanks, Molly. Now for our next question, I'll be directing that to Jinny. Jinny, the question is, the guidance document states that FDA will periodically reassess the list of device materials and exclusion characteristics identified in the tables. How often does FDA perform, or I'm sorry, how often will FDA perform or consider proposals to update the list of included materials, and what are the criteria for inclusion of materials on this list?

**Jinny Liu:** Hey, good afternoon, everyone, this is Jinny Liu. I'm a chemistry reviewer from OPEQ. Thank you for participating in the webinar. And thank you, Kim, for the question.

So, for your question, so the materials listed in Section B are mainly based on the historical use of such materials in intact skin-contacting medical devices. Generally, the chemistry is well understood. And

these materials are commonly used in this type of devices. For each of the materials listed here, we have confirmed the use in medical devices with intact skin contact. But we acknowledge that many polymers, which are not listed in the guidance, may not result in adverse responses if they are used to manufacture intact skin-contacting devices. However, such materials may not be commonly used for intact skin-contacting medical devices, or they are not proposed during the commenting period for this guidance update.

As of right now, the frequency of reassessment has not been determined yet. It will depend on how the standard is used and how many proposals that we will receive for material considerations. As noted in the guidance, comments can be submitted to the docket to suggest the addition or removal of a device material from the list.

So, if you are interested in suggesting the addition of a material, we recommend that the following information be included, the generic chemical name, the identification of FDA medical devices product codes where the material is commonly used with intact skin, and also, please also include a specific rationale for why the proposed materials pose no biocompatibility risk for intact skin.

I hope that answers your question. Thank you.

**CDR Kim Piermatteo:** Thanks, Jinny. We will now take our first live question. Our first live question is coming from Rong. Rong, I have unmuted your line. Please unmute yourself and ask your question.

Rong, are you able to unmute your line?

Alright, hearing none, I'm going to move down to the next hand. The next person I'm going to call on is Michelle. Michelle, I have unmuted your line. Please unmute yourself and ask your question.

**Michelle Lott:** Hi, there. Thanks for the webinar and the information. I had a question about where you said to document this. You referenced, and it's in the eSTAR, as well as the presentation, to document this in the Device Master Record. But it's my understanding that the Device Master Record is the compilation of the procedures and specifications for the actual finished device, whereas the Device History File sounds more like the compilation of the records that make the design history of the finished device. What you said to document seems like it would be something that's more common in the Design History File, and specifically even within a risk management file. So, I was a little unsure why the context of the Device Master Record versus the Device History File.

**CDR Kim Piermatteo:** Thanks, Michelle. Jen, would you like to take a first response for this?

**Jennifer Goode:** Sure, thanks so much for the question, Michelle. So, we are not necessarily experts, the folks on our panel, with how a manufacturer documents things in their records that they have back at their site. So, this went through our legal clearance, and they've confirmed that Device Master Record is the appropriate place. I think that we can look into this a little bit more and follow up. But this is what we were told was the proper thing to include. So, I'm sorry I can't give you a more specific question at this-- or more specific answer at this time.

**CDR Kim Piermatteo:** Thank you, Jen, and thank you, Michelle, for that question. If you have follow-up, please feel free to email DICE if you would like additional clarification, as well, we may be able to look into that for you also.

Alright, our next question is coming from Tobi. Tobi, I've unmuted your line. Please unmute yourself and ask your question.

Tobi, are you able to unmute your line?

Alright, I'm going to move down to the next hand. Next, I'd like to call on Steven. Steven, I have unmuted your line. Please unmute yourself and ask your question.

**Steven Pollack:** Hi, can you hear me?

**CDR Kim Piermatteo:** Yes, I can.

**Steven Pollack:** Terrific. In the materials that were qualified for use in this approach, you used the term polyurethane, and you gave the example of Lycra. Polyurethane is a pretty broad term. Are there any particular polyurethanes that you're thinking about outside of the fabric-based ones? Or is it a very general term?

**CDR Kim Piermatteo:** Thank you, Steven, for that question. Jen, would you like to take, to provide a response for this one, or open it up to the team?

**Jennifer Goode:** I think maybe Jinny can answer this question.

**CDR Kim Piermatteo:** Great. Jinny?

**Jinny Liu:** Hey, Steven. Thank you for the question. So, we definitely recognize polyurethane is a big product families. In this document, we did not call out each of them. So, it applies to typical, commonly used polyurethanes that are used to fabricate this type of device. But if you have some novel polyurethane, you may want to discuss with the Agency before you apply this approach.

**CDR Kim Piermatteo:** And, Jinny, just to clarify, you mean discuss with the Agency like through a Q-Submission, right?

**Jinny Liu:** Yes.

**CDR Kim Piermatteo:** Yeah. OK, thank you, Jinny, for your response. Thank you, Steven, for the question.

And the next person I'm going to call on is Kellie. Kellie, I have unmuted your line. Please unmute yourself and ask your question.

**Kellie Myers:** Hi, my question was about, you said when the patient is not able to notice adverse events, we should put a warning in the labeling, well, a precautionary statement, and you gave some wording for that. I was just wondering; do you have a timeline in mind for when we need to implement this retroactively on existing IFUs and user manuals? Or is that just going forward?

**CDR Kim Piermatteo:** Thanks, Kellie, for that question.

**Jennifer Goode:** I can answer this. This is Jen.

**CDR Kim Piermatteo:** Thanks, Jen.

**Jennifer Goode:** So, the labeling statement is for submissions where you may be using this approach moving forward. And so, we include a recommended statement. If that doesn't seem to work for your particular devices, you can work that out with the review team with your submission, but this is not a retrospective ask, this is a moving forward ask.

**Kellie Myers:** Thank you.

**Jennifer Goode:** I hope that answers your question.

**Kellie Myers:** That's great. Thank you.

**CDR Kim Piermatteo:** Thank you, Kellie. And thank you, Jen. Our next question is coming from Sarah. Sarah, I have unmuted your line. Please unmute yourself and ask your question.

**Sarah:** Thank you for this webinar. So, one of the things in this guidance, it talks about not needing a detailed rationale, but it also talks about a literature search, such as for adverse events. It seems like the FDA has already done that, but the guidance seems to suggest the manufacturer needs to do that as well, which seems like duplicative work and not in the alignment with the least burdensome approach, as the FDA has already done this. Is this supposed to be just a statement? Or is this supposed to actually require a duplicative search on the part of the manufacturer, as compared to what the FDA has already done?

**CDR Kim Piermatteo:** Thanks, Sarah. I'm going to turn it over to Jen to provide you a response.

**Jennifer Goode:** Hi, Sarah. Thanks for this question. So, part of what we were thinking about with this part of the guidance document is we publish a list on a certain day and time. And we did this in September of 2023. In your documentation, in your own Device Master Record, you would, as you're bringing new products to market, be expected to do a literature review to double check that nothing new has come up in the literature or in your device marketed MDRs. And so, we are not asking you to redo the work we've already done, we're asking you in the point in time when this is applied to do a double check and make sure you've addressed what you need to address in your Device Master Record.

I hope that helps.

**CDR Kim Piermatteo:** Thanks, Jen, for that response. Our next question is coming from Devaki. Devaki, I've unmuted your line. Please unmute yourself and ask your question. Devaki, are you able to unmute your line?

Hearing no response, I'm going to move to our next caller. The next hand raised is from Kyoung. Kyoung, I've unmuted your line. Please unmute yourself and ask your question.

**Kyoung:** Thank you. For a device where the intended use is intact skin, however, there is a recognized risk of contact with breach or compromised skin, is this approach still feasible?

**Jennifer Goode:** Can you clarify what an example of that device might be?

**Kyoung:** So, for something that is intended for long-term contact, so it is attached, and there is a potential for just pressure marks or pressure on the skin that could lead to breach or compromised skin. This is a known risk for the device, but not intended to be used, right, on skin that has been irritated or is open. Is this approach still, does that risk necessitate a different approach? Or would this be something to take to a Q-Sub?

**CDR Kim Piermatteo:** Thanks for the clarification. We're looking at Jen or Molly, who's going to help address your question.

**Jennifer Goode:** Sorry, I'm having problems with my mute and unmute as well. This is Jen. I'm happy to take this question.

So, I think that if you have been in conversations with the Agency where you need to address a risk of pressure and aggravation, I think of that more as an adverse mechanical irritation, and not necessarily a biocompatibility issue up front. I think that you may want to clarify that with your review team, but it seems to me that if your only submission issues historically have been cytotoxicity, sensitization, and irritation for intact skin-contacting devices, and you're applying the device to intact skin, I think this policy would still apply, but you may want to double check that with your review team.

**CDR Kim Piermatteo:** Thank you, Jen. Thank you, Kyoung, for your question.

Our next question is coming from Amargit or Al. I've unmuted your line. Please unmute yourself and ask your question.

**Amarjit (Al) Luniwal:** Oh, hi. Can you hear me, OK?

**CDR Kim Piermatteo:** Yes, we can.

**Amarjit (Al) Luniwal:** Oh, thank you, Jen, for a nice presentation. So, my question is about reprocessed single-use devices. Those devices are listed as exclusion. And the reason being is that there is a potential for residuals that could cause irritation. So, my question is, if that is the risk, then could I just do an irritation study or address that irritation risk, and then not necessarily have to do the other two tests because that risk is already being addressed if my device is made up of the materials that are listed in Section B?

**CDR Kim Piermatteo:** Thank you, Al, for that question. Molly, would you like to start by providing a response? And anyone else who has anything to add, they can join in.

**Molly Ghosh:** Yes, this is Molly. So, I think maybe if you could repeat the question?

**Amarjit (Al) Luniwal:** Yes, so my question is, because reprocessed devices have potential for irritation, then is that the only risk I need to address for doing testing or by other means? Or I have to address all three, cytotoxicity, sensitization, irritation, for risk mitigation for those type of devices?

**Molly Ghosh:** So, if you, you know there could be more than just irritation risk, depending on the chemical use for reprocessing. And, you know, in our slide, we just provided that endpoint as an example. So, you have to assess all three endpoints, not just one.

**Amarjit (Al) Luniwal:** OK, thank you.

**CDR Kim Piermatteo:** Thank you, Al, for that question. Our next question is coming from Helin. Helin, I've unmuted your line. Please unmute yourself and ask your question.

**Helin Raagel:** Hi, thank you. My question is related to how much detail is needed on the manufacturing process side that would supplement the Attachment G submission.

**CDR Kim Piermatteo:** Thank you, Helin. Team, I think this is a question about, you said manufacturing, right, Helen?

**Helin Raagel:** Yes, yes. We were talking about the materials and materials that are listed. We'll do a review, double check that there's nothing adverse happening with the material, but then I remember Jen mentioned it in the webinar that also the manufacturing process needs to be reviewed. So, I wanted to know how much detail on that is needed in order to do the submission through that Attachment G clause.

**CDR Kim Piermatteo:** OK, thank you for clarifying. Jinny, would you like to provide a response?

**Jinny Liu:** Sure. Thank you for your question. So, I think, as you say, from the guidance, we're really not asking a lot of detailed information when you are putting together the manufacturing information. I think we just need, you have internal record to show, you have addressed biocompatibility for such device through some of the information, either they are acquired from biocomp testing or the manufacturing information. So, we give you some of the starting points to think about what kind of manufacturing information, I think it will guide you to say what kind of information you are looking for.

For example, when you are doing the manufacturing, I think the, when you are doing the manufacturing process, you, of course, have to purchase and control. So, you just have to think about if you are using the certain type of polymer in your device manufacturing, you have thinking about if the biocompatibility would be a risk for this type of materials or this, if you have sufficient control in place. It's really not an additional ask for when you are managing the manufacturing process, it's just to confirm from all the information you have in-house to make sure the biocompatibility of the device has been assessed.

**CDR Kim Piermatteo:** Thank you, Jinny. Jen, did you have something you wanted to add?

**Jennifer Goode:** Yeah, so I think this is a really good question. I just wanted to make one clarifying point. So, what we're doing with this guidance is, we're trying to shift premarket review issues to the manufacturers to document in their records. And we would not be looking at those details of

manufacturing if this Attachment G approach is used properly. But what we are asking is that as a part of your submission as a manufacturer, you state, I've checked all of my various controls, and you cite your regulations. So those slide examples that I gave is just a yep, I've checked these, I think it's five different things, with the cited regulations. And I've documented this appropriately in my files.

So, we're not asking you for the details of any manufacturing if this approach is being used. We're asking you to document it and to think about these things and include a statement that says, I've thought about these things, and it's in my documentation, so the FDA doesn't need to worry about it. Does that help?

**Helin Raagel:** Yes.

**CDR Kim Piermatteo:** Great.

**Helin Raagel:** Thank you.

**CDR Kim Piermatteo:** Thanks, Jinny. Thanks, Jen. Thanks, Helin, for the question.

Our next question is coming from Kimberly. Kimberly, I've unmuted your line. Please unmute yourself and ask your question.

**Kimberly Ehman:** Thank you very much. Can I ask a question outside of the intact skin contact?

**CDR Kim Piermatteo:** Today's webinar specifically is for the topic of this guidance and these updates. So, we will refrain from asking questions outside of that scope.

**Kimberly Ehman:** Well, it's in the guidance. It's just not related to intact skin.

**CDR Kim Piermatteo:** OK, well, ask your question. We can see, yep.

**Kimberly Ehman:** Alright. So, I don't think this is in the last version of the guidance, but there's a statement under Table 1A that says, the choice of a subchronic or subacute should be related to the duration of device use. And then it says, for example, devices used for greater than 14 days should not be assessed using a 14-day test, which conflicts with Part 11. So, I just wondered if that was the intent. I mean, typically, you could use a 14-day subacute subchronic test for prolonged or even long-term duration to address subacute and subchronic. So, I'm kind of curious as to the intent of that. And if that is the intent, that anything greater than 14 days of exposure, you would not be able to use a 14-day subacute subchronic study.

**CDR Kim Piermatteo:** Thanks, Kimberly. I'm going to turn that over to Jen to provide you a response.

**Kimberly Ehman:** Thank you.

**Jennifer Goode:** So, Kim, thank you so much for the careful reading of the guidance. This is one of the revisions to the guidance that we weren't featuring in the webinar today, but we're happy to address.

So, for folks who have the guidance open, you may know that we used to have a lot more differences in what was in 10993-1 versus what's in our guidance. And there are a couple of O's left, and then there's these two statements that explain some differences. And part of the reason why we did not recognize 10993-1 Annex A was because we were concerned with how long a preclinical study is done compared to how long the intended use is.

So, this statement kind of just puts in writing the fact that if somebody comes in, and their device is used for 28 days, and they give us a 14-day test for this endpoint, and there's no longer test, we may ask for more on that. And so, what we're asking people to think about when they decide how long their subchronic test should be, to think about how long the device is used. And if the device is used for longer than 14 days, we are asking them to consider a longer test. Does that answer your question?

**Kimberly Ehman:** Yes, thank you.

**Jennifer Goode:** I don't know if anybody else wants to add any clarification to that from our team.

**CDR Kim Piermatteo:** Alright. Thank you, Kimberly, and thank you, Jen, for that response. Our next question is coming from Rachel. Rachel, I have unmuted your line. Please unmute yourself and ask your question.

**Rachel:** Hi. Thank you for everyone's time today. My team and I had been discussing during our latest submission that a lot of the biocompatibility guidance, 10993 itself, and then guidance that the FDA issues, is really geared towards the patient. Not a lot about the user/caregiver operating, et cetera. And so, we've noticed also a lot of OUS topics of discussion come out about where really, they're looking for a little bit more of a rationale based on that caregiver use with contacting the device. And so, can you explain in a submission what would be the expectation and consideration to speak to why testing wasn't done for the caregiver? Or also perhaps what testing should be done for the caregiver?

**CDR Kim Piermatteo:** Great. Thank you, Rachel, for that question. Jen, did you want to provide a response?

**Jennifer Goode:** Sure. So, one of the things that we tried to do with our guidance when we actually first issued it in 2016 was to not talk about a patient versus a caregiver, but to actually talk about tissue contact as much as possible. And so, part of the reason that we did this is because we have some devices where there is patient contact and clinician contact, or where there's just clinician contact, or there might be a caregiver contact. And so, components that are in tissue contact, I think that the starting place when we think about things is, is that tissue contact going to be a risk from a biocompatibility perspective.

We do have some devices where we don't ask a lot of questions about users, if they're not clinicians or patients, but we do have some devices if you think about medical gloves or masks that surgeons wear, those primarily contact the clinician, the gloves may contact the patient as well. And so, there are different approaches that have been used historically, but we intentionally wrote this guidance trying to minimize the use of the word patient. I can tell you that we're currently working on a revision with international experts to ISO 10993-1, and one very active point of discussion is how to think about the users, if they're not the patients, if they're clinicians or other caregivers, and how to actually make that issue more clear in the next revision to ISO 10993-1.

So, I would say our FDA guidance tries to be very clear about tissue contact and agnostic as to whose tissue it is. And the 10993-1 revision should have some updates to clarify that language as well.

I hope that helps answer your question.

**Rachel:** It does. Thank you so much.

**CDR Kim Piermatteo:** Thank you, Jen, thank you, Rachel. Our next question is coming from Scott. Scott, I have unmuted your line. Please unmute yourself and ask your question.

Scott, I see that you've unmuted. You may be double muted.

**Scott Feeley:** Hello, can you hear me?

**CDR Kim Piermatteo:** Yes, we can.

**Scott Feeley:** OK, it was asking to allow permission. Thanks for the webinar. Just a very quick general question, is Attachment G dealing with certain devices in contact with intact skin, is this the only update to this final guidance here, this one that superseded the last one?

**CDR Kim Piermatteo:** Thank you, Scott, for that question. Jen, did you want to clarify or provide clarification?

**Jennifer Goode:** Absolutely. So, Attachment G is the biggest edit to this particular revision of the guidance document, but if you go back and look at slide 31 that we presented today, we did identify the fact that there are several other minor revisions that have been made. So, one of the things that we've heard is that we've updated the guidance a few times, but we didn't update the standard revisions that we recognize. So, we published the guidance. A standard was updated. So, it's not 2009 version of the standard, it's 2018 version of the standard. So, with this revision, we made sure every single standard that we reference had the correct revision date, or the date was removed because the standard was revised, but it still addresses something. In some cases, we were quoting statements and standards. So those quotes may have been changed slightly with the new revisions. We also, as we noted, released a guidance earlier this year that talks about animal studies and so how we talked about GLP in this guidance was changed.

We also since the guidance was last revised, we've started a program on ASCA, and so we added a statement about ASCA because how ASCA summary test reports are provided, a full test report is no longer needed. So, we tried to, at a very high level on slide 31 of the presentation, which you'll be able to look at after as well, we tried to outline the kinds of changes that we made so that you could see. But it's worthwhile to go back through and read it again, because there may be some things, we think they're minor, but there may be some things that are important for you to see and understand.

**Scott Feeley:** Thanks so much, Jen. That answers the question.

**CDR Kim Piermatteo:** Thank you both. Our next question is coming from Brian. Brian, I have unmuted your line. Please unmute yourself and ask your question.

**Brian Sidow:** Yeah, thanks for the information. Just had one question. Would the method of sterilization possibly influence the exclusion of an intact skin-contacting device?

**CDR Kim Piermatteo:** Thank you, Brian, for that question regarding sterilization. I'm going to look to Jen, did you want to start, or Simona?

**Simona Bancos:** Yes, hi, this is Simona. Yeah, I can start, and if my colleagues want to add anything to the question.

Yes, you are correct, Brian, and thank you for your question, that sterilization is one type of manufacturing process that can impact the biocompatibility of a medical device material. I wanted to quickly point to Section D of Attachment G, where it states that, or it is recommended that companies are responsible for documenting in their Device Master Record how they have identified and address the biocompatibility risks for their device, including manufacturing. So, for example, as described under 21 CFR 820.70, item B, each manufacturer shall establish and maintain procedures for changes to a process, and such change shall be verified before implementation, and this activity shall be documented.

I hope that that helps to address your question.

**CDR Kim Piermatteo:** Thanks, Simona, for that response. Thank you, Brian, for your question.

Our next question is coming from Elisabeth. Elisabeth, I have unmuted your line. Please unmute yourself and ask your question.

**Elisabeth Hirth:** Hi, can you hear me?

**CDR Kim Piermatteo:** Yes, we can.

**Elisabeth Hirth:** Awesome. Thank you very much for organizing this great webinar, and great questions, great answers. My question is related to also the attachment, Attachment G. I was wondering, regarding the materials, if I have a copolymer made of these materials, is that also, then, applicable, or not?

**CDR Kim Piermatteo:** Thanks, Elisabeth. It looks like, Jinny, I'm going to come to you for a response first. Again, if anyone else has anything else from the team to chime in, please feel free.

**Jinny Liu:** Thank you, Elisabeth, for question. So, if they are a polymer plant, I think they are. And also, the blend of polymer on the list of the section B list, they can apply this approach. But for copolymer, I think we may have to, you may want to discuss with the review team first because the copolymer, if they are not listed in section B, the polymer synthesize can be quite different. And also, we may not have seen such copolymers being used for the intact skin device. So that may be challenging to say if there are going to be risk, can be low. Hope that answered your question.

**Elisabeth Hirth:** Yes, thank you very much.

**CDR Kim Piermatteo:** Thanks, Elisabeth. And thanks, Jinny.

Our next question is coming from Brent. Brent, I have unmuted your line. Please unmute yourself and ask your question.

**Brent Huberty:** Thank you, and thank you, guys, very much for having this seminar, this is really good. The question I have is, if we have an externally communicating device with intact skin components, because of the term and the scope of Attachment G is devices and components, can we use this framework to address the biological risks for the intact skin components of the otherwise classified externally communicating device?

**CDR Kim Piermatteo:** Thank you, Brent, for that question. I am going to look at Molly first, if you would like to provide a response.

**Molly Ghosh:** Yeah. Hi, Brent, this is Molly. Thank you for your question. So, I think if the intact skin is intact skin-contacting parties is evaluated separately from the entire device, then I think you could still use the Attachment G approach.

Did that answer your question?

**Brent Huberty:** Am I still unmuted?

**CDR Kim Piermatteo:** Yes, you are.

**Brent Huberty:** OK. I'm not sure what you mean by evaluated separately. I mean, if they were all part of the same device, and the overall device was categorized as an externally communicating device, let's just say a delivery system that had, say, for example, a handle on the outside of the patient that could potentially come in contact with intact skin. A way to not have to, or maybe lessen the amount of testing specifically for cytosensitization and irritation on those parts that are intact skin contacting.

**Molly Ghosh:** Yeah, thank you for the clarification. And Jen, please feel free to add. So, if that handle currently is evaluated only for those three endpoints versus for an external communicating, depending on the contact duration, you might have, you have to do more endpoint testing. So, if that handle is tested separately now for those three endpoints, I think you could still use that Attachment G approach for that handle part.

**Brent Huberty:** Got it. So, it would be logical to exclude the intact skin testing portions from the other tests other than those three, and use Attachment G for the intact skin portions of the device?

**Molly Ghosh:** Yes.

**Brent Huberty:** Got it.

**Molly Ghosh:** Jen, do you have anything to add?

**Jennifer Goode:** Yeah, so the one thing that I want to just caution people about, whether you're doing testing or a rationale for the other components that are not a part of this Attachment G policy, you need to think about whether the joining of that intact skin contacting to the other parts of the device could impact the biocompatibility of the other parts of the device. So, if you're doing your assessment on the

final sterilized device, that's fine, but if you're thinking about the components separately, you just have to remember that that joining process could impact things. So just to keep that in mind.

**Brent Huberty:** Got it. Thank you very much.

**CDR Kim Piermatteo:** Thank you all. Our next question is coming from Tobi. Tobi, I have unmuted your line. Please unmute yourself and ask your question.

**Tobi Fagbohun:** Yes, hello. Can you hear me?

**CDR Kim Piermatteo:** Yes, we can.

**Tobi Fagbohun:** Awesome. Thank you so much for the webinar today. I had a question as it relates to skin contacting device. What is the standpoint of the applicability of 10993-1 to secondary packaging components, such as packaging cartons, labels, and IFUs that may contact the user's intact skin during the use of the device?

**CDR Kim Piermatteo:** Thanks, Toby. So, you're talking about secondary materials, correct?

**Tobi Fagbohun:** So secondary packaging

**CDR Kim Piermatteo:** Packaging

**Tobi Fagbohun:** Like so for a combination product, such as an autoinjector, it sits within a carton, and the carton has labels, and there's an IFU. Are these in scope of 10993-1 when it comes to the biocompatibility assessment?

**CDR Kim Piermatteo:** Sure, thank you for clarifying. Jen, would you like to provide a response?

**Jennifer Goode:** Sure. So, we are not, from a regulatory perspective, asking people to individually assess secondary packaging. What we are asking people to assess as a part of our biocompatibility guidance is the final sterilized device. So, if primary packaging is touching the device, there's a potential for that to impact the biocompatibility of the device.

Secondary packaging is not in contact with the device. So, I'm not sure how that would apply. That's not a part of our regulatory review. I'm not sure if anybody else has any clarifications they want to add to that.

**Molly Ghosh:** I can add. This is Molly. So, I think when we recommend biocompatibility testing, we recommend testing our assessment on the final finished device, which includes the device if it's packaged, sterilized. So, the final finished device means device inside that sterilized package that's being tested. So, if anything transferring from the packaging to the device, that would be tested in the final finished device testing.

**Tobi Fagbohun:** Can I ask a clarifying question?

**CDR Kim Piermatteo:** Sure, go ahead.

**Tobi Fagbohun:** So, in a situation where the final finished device is not sterilized, like a combination product that has a biologic drug inside of it, would this recommendation still apply where then you, because there isn't any sterilization, you wouldn't be assessing what that looks like between the secondary packaging, like the carton that the device is in? And the device itself.

**Jennifer Goode:** So, when we review products-- I'm just going to generically answer this question, not about a combination product. When we review products that are provided to the user non-sterile, and they need to be sterilized prior to use, that sterilization is assessed in the regulatory review that we conduct. So, the manufacturer would have recommendations for how that should be sterilized, and we would look at that potential impact. So, from a biocompatibility perspective, if a device is provided, and it needs to be sterilized prior to use, the manufacturer would provide instructions on how that should be sterilized, because the device may or may not be compatible with all methods of sterilization. And those sterilization procedures should be used on the device prior to the biocompatibility assessment.

Again, the secondary packaging does not contact the medical device, then it's not relevant. If it contacts the medical device, it's relevant. We are not asking people to do separate biocompatibility assessments of packaging. We're asking people to assess the medical device that will be provided to the user and whatever it contacts along the way for packaging, then that would be a part of the device in its final finished form as it's provided to the user. Hope that helps.

**CDR Kim Piermatteo:** Thanks, Jen. Thanks, Tobi. Alright, our next question is coming from a number. The number is 3544045. I have unmuted your line. Please unmute yourself and ask your question.

**Anu:** Hello. Thank you for the opportunity for to ask the question. Can you hear me clearly?

**CDR Kim Piermatteo:** Yes, we can. Just make sure you speak up, OK?

**Anu:** OK. So, my question is around color additives. I know it was mentioned before that you can list the names of additives. So, my question is in the premarket application, how much detailed information about color additives is expected for a device that is expected to have contact for less than 24 hours?

**CDR Kim Piermatteo:** Thank you. I apologize. I didn't catch your name. Did you, what's your name?

**Anu:** My name is Anu.

**CDR Kim Piermatteo:** Anu?

**Anu:** Yeah.

**CDR Kim Piermatteo:** OK. Thank you, Anu. Alright, Molly, would you like to provide Anu a response?

**Molly Ghosh:** Yes, sure. And thank you for the question, Anu. So, for intact skin-contacting devices with limited or prolonged contact, which means up to 30 days of contact, only, as long as you provide us the name of that color additive, that should be sufficient. Intact skin-contacting devices with long-term contacts, meaning greater than 30 days of contact, there will be additional information to be submitted. And on page 61 of our guidance, there is a link to our webinar, which kind of specifies what kind of

information that needs to be provided for the color additive if the contact duration for that device with intact skin is greater than 30 days.

**Anu:** OK, thanks.

**Molly Ghosh:** There is a link. You can just click on that link.

**Anu:** Yeah. The question around the name, is that a manufacturer name, or is that a CLS number? Because sometimes that is the proprietary information and it's difficult to get it from the manufacturer of the material.

**Molly Ghosh:** So, for the long-term implant, long-term intact skin-contacting devices, we ask for chemical name or GASH numbers. So, as you will see, if you go to that link, it provides more details of what kind of information that needs to be provided.

**Anu:** OK, thank you.

**CDR Kim Piermatteo:** Thanks, Molly. Thanks, Anu, for your question. Our next question is coming from Roberto. Roberto, I've unmuted your line. Please unmute yourself and ask your question.

**Roberto Cunha:** Hi, it's a clarification. The new guidance does not reference 10993-23, which has been partially recognized. And it does reference this new guidance from September, right? So, is there a reason for not being identified on the guidance? I don't know if it's because of the dash-10's transitional period. So, if I'm submitting, so what is the FDA current thinking on the 10993-23, or if there is a reason for not being identified on the guidance?

**CDR Kim Piermatteo:** Thanks, Roberto, for that question. Jen, I'm going to turn it over to you.

**Jennifer Goode:** Yeah, so this is a great question. So, the guidance, we don't in the guidance list all of the standards that we do or don't recognize. This is because standards change over time. And so, what we're doing in this particular guidance is we're only listing those standards where there some point that we want to make in terms of what we're saying in the guidance and how it relates to a standard that you also may be using.

And so, if we have a direct quote, we're going to reference a standard. Or if there's a concept that we often ask questions about, and you can look for more details in a recognized standard, then we'll cite the standard there. And so, this guidance doesn't say everything about the biocompatibility review universe. It just really is laying out the issues where we've, in the past, had a lot of questions that we're hoping if we write it down in guidance will then give our stakeholders transparency so that they can come to us prepared to address that issue in some way.

So the way in which to know exactly what standards FDA recognizes, either in full or in part, for biocompatibility, we ask people to go to our Recognized Standards Database, look up the standard by the number, and look at the supplementary information sheets to see, is this a full recognition, is this a partial recognition, or is it not even in that database because we don't recognize it at all?

We would be spending a lot of time updating the guidance every time a standard changes otherwise. So really, we already have a database that outlines what we do and don't recognize in the standards. And so instead of putting every detail in the guidance, we ask you to go to our database to find that information.

**Roberto Cunha:** Thank you. In that case, we follow the transitional timeline, right? So, until December 2024, we use the previous dash-10, and then the dash-23.

**Jennifer Goode:** So, the way the transition works is at the point in time when we recognize it, you can cite it. If you want to cite the old revision to a guidance, that's what the transition period applies to. We ask that people don't keep citing the old version of the standard if a new one has been developed and recognized. And so, the transition period doesn't have to do with the new revision. It has to do with citing the old revision.

**Roberto Cunha:** Thank you.

**Jennifer Goode:** Yep.

**CDR Kim Piermatteo:** Thank you, Roberto, for that question. And thanks, Jen, for your response. Our next question is coming from Ted. Ted, I have unmuted your line. Please unmute yourself and ask your question.

**Ted:** Hi, yeah, this is a question going back to the work required to understand material evaluation. So, this is a little more specific to class I devices. So, it's not 510(k). It's 510(k) exempt and typically GMP exempt. But the question is, how do you kind of do that material analysis? Can we write down those cast numbers, give that material information, give the SDS's, and maybe look at our complaints, and maybe look at any adverse events reported for these products? And if we don't find anything, then can we call that material good as long as it's listed in Attachment G? Or is there something else that we should provide?

**CDR Kim Piermatteo:** Thanks, Ted. Jen, would you like to begin providing a response, or would somebody else from the team like to chime in?

**Jennifer Goode:** Yeah, I can start. This is Jen Goode. So, for class I exempt devices, FDA and our guidance is not designed to deal with class I exempt devices. Our guidance is designed to deal with devices where you would need to submit to us. So, we know that manufacturers take different approaches to how they record things in their files that they keep at their site. So, for class I exempt devices, you're not submitting to us.

Now, you can use the approaches described in our guidance to document in your Device Master Record how you've addressed things. I think Attachment G does speak to the parts of the regulation you're responsible for, even if you don't submit to us. And that level of detail that you include in those records that you keep in-house should be the level of detail that you think is appropriate to support that the biocompatibility, for example, does not present an inappropriate risk, that you've addressed it however you think is appropriate.

**Ted:** Thank you. I know it's a little bit complicated when it comes to class I devices because we don't report 510(k)s, but I appreciate your feedback. Thank you.

**Jennifer Goode:** Thank you as well.

**CDR Kim Piermatteo:** Thank you, Ted. And thank you, Jen. Our next question is coming from Vivek. Vivek, I've unmuted your line. Please unmute yourself and ask your question.

**Vivek Raut:** Hi, thank you for the opportunity. So, I saw that in the Attachment G, you included some of the non-synthetic polymer components, such as cotton or the silk fiber. What about the extracellular molecules, like hyaluronic acid, hyaluronan, elastin, or collagen, that can be applied on the intact skin? Are they excluded from the new attachment guidance or included?

**CDR Kim Piermatteo:** Thank you Vivek for that question. I believe you're referring to, are you referring to animal materials, Vivek? I'm sorry. I wanted to clarify that.

**Vivek Raut:** Yes. Yes

**CDR Kim Piermatteo:** OK.

**Jinny Liu:** Hey, thank you for your question. So, as you can see, there are several materials have been excluded, like gel cream biologics. So, I think we explained in our guidance there is some additional risk presented by those materials. I think it may not be applicable for this guidance if the device are, I mean, if the materials are excluded.

**Vivek Raut:** Understood. The reason I got sort of alarmed because the silk is also a biomaterial that was previously required to complete all the biocomp testing, but I understood where the positioning is for the animal-derived materials. Thank you.

**Jennifer Goode:** So, if I could add to this, this is Jen. So silk is explicitly included. Everything in the synthetic polymers and natural fabrics list, previously, someone had to do a full biocompatibility assessment on, either testing or a rationale. So, everything in the list in Section B, we've said you don't need to worry about that. We do have a section in Attachment G that says there are some things that you need to come and talk to a specific review team through the Q-Submission process. And one of those things is biologics. So, if you have a biologic that's not in the list, and you would like to apply this, so you talked about collagens and hyaluronic acid. You need to talk to your review team to see if they think that this particular approach is something that they're willing to accept or if they'd like you to continue to do the traditional approach.

**Vivek Raut:** Understood. Very good, thank you.

**CDR Kim Piermatteo:** Thank you, Vivek, for that question. Our next question is coming from Meryem Demir. I've unmuted your line. Please unmute yourself and ask your question.

**Meryem Demir:** Hello, can you hear me?

**CDR Kim Piermatteo:** Yes, we can.

**Meryem Demir:** Thank you for this webinar. I have a question about the Attachment G included material list. We know that there are certain materials in the list that typically fail cytotoxicity, especially when tested using MEM elution, despite their long history of safe use. So, I'm sure your FDA is aware of that fact. So, could you please provide some insight how to apply this approach for such materials?

**CDR Kim Piermatteo:** Thank you, Meryem, for that question. Yeah. I think, Molly, would you like to provide a response first?

**Molly Ghosh:** Yes. Thank you for your question. So, the material listed in Attachment G, we looked into the history of the materials and use of these materials in the devices and the intact skin-contacting devices, you have to address three endpoints. And those endpoints were addressed for those intact skin-contacting devices and when we are looking into the material list and the history of use, we took into consideration the data that we have received. And then I think for, I think, as Jen said in her talk, that if there are history, if there are some documented history of the failure or adverse reactions, I mean, there is a Q-Sub process that is recommended to come and talk to the review team.

**Jennifer Goode:** So, if I could just add to this, so our expectation is that some materials may, are expected, most materials are expected to pass. There may be some materials that have a certain level of, for example, cytotoxicity that would be expected based on the materials. But if you, for your particular device, have a high level of toxicity, before you come in with a proposal or a submission using this, we do, in our list of topics which we recommend you talk to the team for a Q-Submission include, if you've previously for your device had a toxic result, we want you to go and talk to the review team using the Q-Submission process, just to make sure that the approach is acceptable.

So let me, for an example. So, if a device includes a surfactant, and those devices always have surfactants, those surfactants can cause a cytotoxicity failure. And you might see that device area, now, I'm just totally making this up, this is hypothetical, grade 3 cytotoxicity all the time. Well, we don't need to see that again necessarily. But you need to double check with your review team for those devices.

If you're getting a grade 5 cytotoxicity, where before you had a grade 3 cytotoxicity, that could be a flag for you that something else is going on that needs to be resolved. So, we really can't say that's going to be in or out. You have to really talk with your review team about that.

**CDR Kim Piermatteo:** Thank you all. Thank you, Meryem, for that question. We have time for a couple more questions. Next, I'm going to call on Ar. Ar, I have unmuted your line. Please unmute yourself and ask your question

**Ar:** Oh, thank you. So, I think this is a brief question. At what point is, is abraded skin intact skin? And if not, at what point is it not intact skin?

**CDR Kim Piermatteo:** I apologize. Did you say "braided"?

**Ar:** Abraded.

**CDR Kim Piermatteo:** Abraded, thank you. Alright, thank you for that question.

**Molly Ghosh:** Hi, this is Molly. I can take this one.

**CDR Kim Piermatteo:** Thanks, Molly.

**Molly Ghosh:** Thank you for your question. Abraded skin is not considered intact skin. It's a compromised skin. So, then Attachment G approach cannot be used for skin that is compromised.

**Ar:** OK. I wasn't concerned about Attachment G. I was just wondering per 10993, do you look at abraded skin as compromised or intact?

**Molly Ghosh:** So abraded skin is considered not an intact skin. It's a compromised skin.

**Ar:** OK, thank you.

**Molly Ghosh:** Hope that helps

**Ar:** Yes.

**CDR Kim Piermatteo:** Thank you for that question. Thanks, Molly. Alright, our next question is coming from Taieb. Taieb, I've unmuted your line. Please unmute yourself and ask your question.

Taieb, are you able to unmute your line?

Alright, we are going to go ahead and move down to our next question. Our next question is coming from Claus. Claus, I've unmuted your line. Please unmute yourself and ask your question.

**Claus Soendergaard:** Hi, can you hear me?

**CDR Kim Piermatteo:** Yes, we can.

**Claus Soendergaard:** OK, this is for the general updates, not Attachment G. So throughout, you've updated the language from previously, like in talking about long history of safe use, from talking about legally U.S.-marketed devices, to now just calling out legally marketed devices. So, my question is if that is to be interpreted that there's a greater opportunity to leverage OUS marketed devices and biocompatibility evidence for safety assessments.

**CDR Kim Piermatteo:** Thank you, Claus. I'm going to turn this over to Jen.

**Jennifer Goode:** So, I'm actually looking in the guidance document for the first footnote related to legally marketed devices. We are, so if you'll just give me a second, so I can tell you what page it's on and what number it is. OK, so on page 4 of the guidance document, footnote number 10, there is a footnote that says, "For the purposes of this guidance, legally marketed devices are limited to devices marketed in the U.S." So, we made a change throughout the guidance to remove the U.S. legally marketed devices and include just this first footnote number 10 on this topic. Does that help?

**Claus Soendergaard:** Yes, thank you for clarifying.

**CDR Kim Piermatteo:** Thank you, Claus, for that question. Thanks, Jen, for the clarification.

Alright, we have time for one more question today. I'm going to call on Alex. Alex, I have unmuted your line. Please unmute yourself and ask your question.

**Alex Yang:** Hi, thanks for taking my question. Actually, my question is about degradation. In section 5B, it mentions that you can do in vitro degradation testing with a technical rationale to not, I guess, do in vivo testing. I'm wondering if you're already doing in vivo testing that's assessing local and systemic toxicity. Is that considered to supersede in vitro testing for degradation?

**CDR Kim Piermatteo:** Thank you, Alex, for your question. I'd like to open it up to the team. Anyone would like to provide a response to Alex?

**Jennifer Goode:** So, I'm trying to pull that section of the guidance cause we were not really, we didn't study up on that before we came today. So, can you tell me what page?

**Alex Yang:** Sorry, it's tough. Page 20.

**Jennifer Goode:** Page 20? And so, page 20, hmm-- PDF page 20 or?

**Alex Yang:** Oh--

**Jennifer Goode:** It's page 20, OK. Can you repeat your question again? Now I did find where that is, but...

**Alex Yang:** It presents it as if in vitro testing with a technical justification can sort of be used to address potential biocompatibility issues with degradation products. If we're already doing in vivo testing that looks at local and systemic tox, and degradation is implied in the in vivo aspect of the testing, is that considered to supersede the in vitro testing?

**Jennifer Goode:** So, Jinny, this part of the guidance document is very specific to testing in situ polymerizable, in situ polymerizing and/or absorbable materials. And I know Jinny has some experience looking at these. And so, I'm going to ask her to follow up on my answer in case she has something else.

So, what I want to say about this is I think I understand your question to be, do you have to do both? And I think it may depend on the devices and you may need to talk with your review team through the Q-Submission process.

Jinny, did you have anything else to add to that? I know we're right at 2:30.

**Jinny Liu:** Yeah, thank you, Jen. I think you'd maybe better follow up with the review teams. But typically, we just wanted the biocompatibility endpoint to be addressed. Either they do support it by the in vivo testing or by the in vitro testing. But definitely, I think if you have a novel absorbable devices, you may definitely want to follow up with the review team to make sure your strategy is appropriate.

**Alex Yang:** Alright, thank you.

**CDR Kim Piermatteo:** Thank you, Alex. And thank you, Jinny, and Jen. And I just want to thank everyone right now. That wraps up our question-and-answer segment for today. So, thank you all for your participation.

I'd now like to turn it back over to Jen to provide her final thoughts for today. Jen?

**Jennifer Goode:** Thank you so much, everyone, for participating and for all the great questions that you asked. If there is one thing I'd like to have you take home from this webinar today, it's that the Attachment G part of this guidance now provides a new approach for certain devices in contact with intact skin and we hope this approach can be used to make these submissions more efficient from a biocompatibility perspective and be least burdensome for both you as the submitters, as well as FDA as the reviewers. I hope you all have a great day.

**CDR Kim Piermatteo:** Thank you, Jen, for those final thoughts. And thank you so much for your presentation today. I'd also like to thank Simona, Molly, and Jinny for participating on today's panel.

For your information, printable slides of today's presentation are currently available on CDRH Learn at the link provided on this slide under the section titled Specialty Technical Topics and the subsection Biocompatibility. A recording of today's webinar and a transcript will be posted to CDRH Learn under the same section and subsection in the next few weeks. A screenshot of where you can find these webinar materials has been provided on this slide.

If you have additional questions about today's webinar, feel free to reach out to us in DICE at dice@fda.hhs.gov. Lastly, we hope you're able to join us for a future CDRH webinar. We do have quite a few scheduled over the next two months. And you can find a listing of all those and any of our other upcoming webinars via the bottom link on this slide at www.fda.gov/CDRHwebinar.

Thank you all again for joining us. This concludes today's CDRH webinar. Have a great day.

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