NWX-FDA-OC

Moderator: Irene Aihie
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Coordinator: Welcome and thank you for standing by. At this time all lines are in listen-only mode for the duration of today's presentation. This call is being recorded. If you have any objections, you may disconnect at this time. We will conduct a question and answer session at the end of today's presentation. If you would like to ask a question today, please press star 1.

I will now turn the call over to our host for today, Ms. Irene Aihie. Ma'am, you may begin.

Irene Aihie: Thank you. Hello and welcome to today's FDA webinar. I am Irene Aihie of CDRH's Office of Communication and Education. On June 16, 2016 the US Food and Drug Administration issued a final guidance document, Use of International Standards ISO10993-1 -- "Biological evaluation of medical devices Part 1: Evaluation and testing within a risk management process."

The final guidance allows manufacturers to use the ISO10993-1 standard when assessing the potential biological response of the medical devices and materials that come into direct or indirect contact with the human body.

The focus of today's webinar is to share information and answer questions about the final guidance. Your presenter is Jennifer Goode, a Biomedical Engineer from the Office of Device Evaluation here in CDRH.

Following the presentation, we will open the line for your questions related to the topics in this final guidance only. Additionally, there are other center subject matter experts available to assist with the Q&A portion of the webinar.

Now, I give you Jennifer.

Jennifer Goode: I want to thank everybody for your attendance. I'm going to talk today about the goals we had for this particular guidance on biocompatibility, how the guidance developed over time, the framework we used for this guidance, some key definitions that are important to the guidance and this webinar presentation, when biocompatibility should be considered, the risk-based focus for biocompatibility evaluation, how we're now focused on endpoint assessment rather than testing, some considerations for endpoint assessments, some recommendations for chemical assessment, and then considerations for labeling devices with some type of "dash" free labeling, such as latex-free.

When we first started writing this guidance we wanted to clarify how the FDA was using ISO 10993-1 and also address common biocompatibility testing issues in submissions to the US FDA. And these were noted in the draft guidance that was published in 2013.

Based on comments, we realized that we really needed to expand the guidance to explain how risk management could be used to address biocompatibility and leverage existing testing, if possible. And so that was the focus of the final guidance document that was published earlier this year, and as such most of the webinar today will be focused primarily on this risk assessment piece even

though there are a lot of additional points in the guidance document on the first two items here.

So as most of you probably know, we published the draft in April of 2013 and comments closed in July of that year. We received over 700 comments and we revised the document to be responsive to the comments that were received. Our final guidance was published in June of 2016 and the website information if you aren't able to find it will be in the slide set that will be available after the webinar.

We had comments from 36 groups and individuals including 11 device companies, seven trade associations, four drug companies, three biocompatibility test labs, two standards development organizations, two consulting groups, and one academic institution.

Most of the comments that we received asked for more emphasis on risk assessment and what people could consider instead of doing biocompatibility testing. There were some terminology questions and there were several requests for definitions. We also got many comments on the testing considerations section and the section that we originally included as the chemicals of concern section. And then we had tables and flow charts in our original draft guidance and there were several comments on those as well.

So the guidance as it was published in June includes introduction and scope. There's a new section on risk management for biocompatibility evaluations. There is still some information on how the ISO 10993 part one document and FDA modified matrix coordinate. We have a section on general biocompatibility testing considerations, mostly to do with sample preparation and then some test-specific considerations, chemical assessments, and labeling devices as "dash" free.

In addition, for the attachments we have some new attachments in this final guidance. We modified Attachment A, the "Evaluation Endpoints for Consideration." There is a new attachment on master files for devices and what information is helpful for biocompatibility evaluations. There is a "Summary Biocompatibility Documentation" example in Attachment C which is new. The biocompatibility evaluation flow chart has been modified since the draft. The Attachment E, "Contents of a Test Report" has been modified. Attachment F, "Component and Device Documentation Examples" has been modified slightly. And then there's this new glossary in Attachment G for definitions.

We removed some issues from the draft guidance that we determined would be more appropriate for separate guidances due to the level of detail needed. And these concepts were specific to color additives and the biocompatibility of gas pathway devices.

For the purposes of the guidance document as well as the discussion today, I wanted to walk through a few key definitions.

We consider biocompatibility the ability of a device material to perform with an appropriate host response in a specific situation.

When we talk about direct contact, this term is used for a device or device component that comes into physical contact with body tissue.

When we talk about indirect contact, this is a term used for a device or device component through which a fluid or gas passes, prior to the fluid or gas coming into physical contact with body tissues. In this case the device or device component itself does not physically contact body tissue.

When we talk about devices in their final finished form this term used for a device or device component that includes all manufacturing processes for the to be marketed device including packaging and sterilization, if applicable.

When we talk about novel materials, we're considering materials that have not previously been used in any legally US-marketed medical device.

When we use the term sponsor, we're talking about manufacturers, submitters, or applicants with submissions to the FDA.

And there are another 15 definitions in the glossary in Attachment G.

So we want to talk a little bit about when biocompatibility is considered. This is a critical part of FDA's determination of safety and effectiveness for new and modified devices. So for a new device, if the medical device materials come into direct or indirect contact with the human body, biocompatibility needs to be considered. And for modified devices, if the changes are to any components that have direct or indirect contact with tissue or they could affect another component that has tissue contact, biocompatibility should be considered.

And in the guidance document we include this example of a modified device to help with that understanding of when the modified component doesn't have contact but it could impact biocompatibility anyway. So the example is that a new internal component is added. And this component itself has no body contact. But there is some heat applied to join this internal component to an external component that does have body contact. Because heat could change chemistry, biocompatibility should be evaluated in some way.

We think about biocompatibility issues for all submission types. These include PMAs, HDEs, IDE, 510(k)s, and de novo requests.

When we're looking at biocompatibility compatibility, it's to determine the potential for an unacceptable adverse biological response.

We often use biocompatibility standards to facilitate information submission to the FDA. This guidance document was written in particular to address how ISO 10993-1 and the related 10993 series of standards can be used, but as noted in the document there are other biocompatibility standards from ASTM, ICH, OECD, and USP that can also be used, and the same concepts would apply.

We're going to talk a little more specifically about how to use a risk based approach for biocompatibility. In ISO 10993-1, the users of this standard are asked to consider several key concepts which are outlined here and addressed in the guidance as well. And these are:

- device design, material components and manufacturing processes;
- the clinical uses of the device including the intended anatomical location; the frequency and duration of exposure of the device to the body tissue;
- potential risks from a biocompatibility perspective;
- what information is available to address the identified risks; and
- what information is needed to assess any remaining knowledge gaps, such as new biocompatibility testing or other evaluations that appropriately address the risks.

We note in the guidance that new biocompatibility testing may not be needed if the device is made of materials that have been well characterized chemically and physically in the published literature; and have a long history of safe use.

But materials and manufacturing information is also needed to demonstrate that no new biocompatibility concerns exist.

It may be possible to leverage previously conducted biocompatibility information if:

- the previously tested device has similar indications, type, and duration of contact;
- an explicit statement is provided regarding any differences in materials or manufacturing between the new and leveraged devices under consideration; and
- information is provided to explain why differences aren't expected to impact biocompatibility.

We talk in the guidance quite a bit about endpoint assessment versus testing because this is a common concern for device industry. In Attachment A of the guidance document is the framework we're using for the development of a biocompatibility evaluation and is very similar to a matrix that was included in our previous guidance document G95-1.

This is modified from ISO 10993-1, Annex A in the 2009 version of that guidance document and it is not a checklist for testing. In this matrix, all of the X marks are identified in ISO 10993-1 2009 and recommended as endpoints for consideration. And the O's indicate additional FDA-recommended endpoints for consideration.

Our expectation is that submissions to the FDA would address all X's and O's in the biological safety evaluation. Sponsors can use existing data, additional endpoint-specific testing, or a rationale for why the endpoint does not require additional assessment.

So to reiterate, when we're looking at a biocompatibility evaluation, we do want all the X's and O's to be addressed. But they may not be relevant for all devices in a particular category. We also point out in the guidance document that for novel materials or manufacturing processes, additional evaluations beyond those recommended in Attachment A may be needed. We also note that devices with multiple types of exposure should include information to address each exposure category.

So this is a subset of this table A.1 from Attachment A. And what I've highlighted here is just the section on implant devices and we're focusing here on devices in contact with blood. The contact duration is noted here as A, which is limited, less than 24 hours. And you see a series of X's and O's, and some blank spaces.

So the X's indicate that ISO 10993-1 suggests that there should be some consideration of cytotoxicity, sensitization, irritation or intracutaneous reactivity, acute systemic toxicity, genotoxicity, and implantation. In addition, there are O's under the categories of material mediated pyrogenicity and - sorry, genotoxicity. I read it wrong. ISO recommends implantation and hemocompatibility. And FDA also asks for consideration of genotoxicity. And so that's how this Attachment A matrix can be read.

The guidance also points out that if it determined that some testing is needed, the guidance identifies:

- general testing considerations for sample preparation;
- specific testing considerations for various biocompatibility endpoints such as cytotoxicity; and
- why literature is often used to assess specific endpoints such as carcinogenicity or reproductive and developmental toxicity.

In the guidance document we try to make sure that we addressed points where there were test-specific issues that resulted in deficiencies in many of our premarket submissions.

We point out in the guidance document that our expectation is that your biocompatibility evaluation will consider the device in its final finished form. And if the device is provided sterile from the manufacturer, or it needs to be sterilized prior to use, a sterile device should be used for the assessment.

If the final finished form of the device is not used, the submission to FDA should document any differences. Attachment F includes some example documentation language that may be helpful and it's outlined here.

So there may be a comparison to a test article and we expect that the submission will explain whether or not the final sterilized device was used. And when we're thinking about the final sterilized device, we're talking about formulation, processing, sterilization, geometry, and other chemicals that might have been added during the formulation or manufacture process.

You also can potentially compare your product to a previously marketed device. And so there is example language that can be used in Attachment F for that as well.

In the section on sample preparation, we point out in the guidance document that ISO 10993-12 can be used to determine how much sample to be used. We ask for surface area of the device to the extract volume to be used for extract tests. When extract studies are done, we ask for testing using both polar and non-polar solvents unless it doesn't make sense for the device in question.

There's also information on how to simulate clinical use conditions for extractables and leachables. And so in 10993-12, there are many different conditions that can be used. And depending on your device use, a short extraction may or may not be appropriate -- for example, for a permanently implanted device.

We do ask that extracts be conducted separately for device components that have different durations of body contact. So a delivery system might have a limited less than 24-hour use whereas it may be delivering a permanent implant.

For new materials, we also ask that they be assessed separately from other material components unless there's an appropriate explanation for why that is not needed.

We have several sections on endpoint considerations that are specific to testing if it's done. And so this slide outlines those sections where the information can be found. And I'm just going to spend a few minutes here on this slide highlighting at a very high level some of the points in some of these sections.

In the cytotoxicity section, you will find information on how one might assess novel materials or materials that show cytotoxicity under standard conditions. In the hemocompatibility section is information on how one might use in vitro versus in vivo (thrombogenicity) assessments as well as information on rationales that can be helpful to support omission of complement activation testing, if applicable.

In the pyrogenicity section, is information on material-mediated versus endotoxin-mediated pyrogenicity as there are sometimes questions on whether

these are interchangeable assessments. This section also provides clarification on the types of devices where pyrogenicity assessments should be considered.

In the genotoxicity, carcinogenicity, and reproductive developmental toxicity section, are information on how to use chemical information and risk assessment instead of testing. In addition, the genotoxicity section outlines the rare cases when an in vivo genotoxicity study might be considered.

In the degradation assessments section is information on considerations for in vitro and in vivo degradation assessments, if applicable.

We also have a section on chemical assessments and we point out in the guidance document that additional chemistry information may be needed:

- for support of long history of safe use rationales;
- for devices with unexpected biocompatibility test findings;
- for devices manufactured from materials that intentionally change over time such as in situ polymerizing or absorbable materials;
- for some devices including chemicals with known toxicities such as carcinogenicity, where new biologic testing is rarely conducted;
- for new chemicals used to modify material formulations or device manufacturing processes; or
- for devices made from novel materials.

There are two types of chemical information that might be relevant.

Descriptive information can include chemical identity; composition, formula, formula weight, structural information, and manufacturing and purity information; amount by weight percent and total amount such as micrograms; identity of other devices marketed in the US where the chemical entity has been previously used.

Possible chemistry information sources could include from a material or component supplier. And Attachment B explains how a device master file might be useful to support this.

And then also there's information in the guidance on extractables-leachables testing.

This chemical assessment section also talks about how to look at exposure if chemicals are coming out of the device. And this needs to consider both the chemicals of the material (as well as related impurities) that may be available over time. The consideration for repeat device use may be relevant to a biocompatibility risk assessment. And how to use extractables-leachables modeling or actual chemical analysis testing to optimize estimation of exposure during clinical use.

In addition, a safety assessment of each chemical would be needed. And information sources can include known data from toxicology literature or material suppliers. There's information in the document about how to derive tolerable intake (TI) values or threshold of toxicological concern values for unknowns, if a TI cannot be derived.

There's also a section in the guidance on considerations for "dash" free labeling. We know that there are current methods that people use that actually may not be able to detect an allergen or toxic compound at very low levels that could still produce an adverse effect in a highly sensitive individual. And that's why we have this section in the guidance.

We talk about in the section, labeling statements that wouldn't require testing including:

- "not made with a material such as latex" or

- "this device is not made with latex" or
- "a component is not made with latex."

I want to just point out to you that this is a big team that we had at FDA to work on various sections of the guidance document. And so this slide is to thank all of my colleagues who participated in the scientific content development. And we also had several colleagues who helped with all of the administration pieces that have to happen to make the guidance work. So I want to thank them.

And at this time, we are going to open the call for questions.

Coordinator: If you would like to ask a question, please press star 1, unmute your phone, and record your name clearly at the prompt. Your name is required to introduce your question. To withdraw your questions, you may press star 2. Once again if you would like to ask a question, please press star 1 and record your name at the prompt.

One moment for the incoming questions. We have our first question. (Amanda) your line is open.

(Amanda): Thank you. My question was on the gas pathway devices. Do we have any estimated date for when that additional guidance will be coming out? And also can you speak to how aligned it will be to the new ISO standards coming out for gas pathway devices as well?

Irene Aihie: Once second while we get that answer for you.

(Amanda): Thank you.

Angela Krueger: Hi. This is Angela Krueger. Regarding the timeline for the guidance development on the gas pathway devices, we are currently working on that guidance. We can't give you a definitive timeline for when it will be published. But we are actively working on the guidance development.

(Amanda): Okay. Do you have any commentary on how tightly it will be aligned to new ISO standards coming out? Or is it still in the early stages?

Jennifer Goode: So we've been actively working with the ISO standard that's currently under development and until that's finalized and the FDA guidance is finalized, we can't necessarily comment on how tightly they'll be aligned.

Our hope is that the standard itself will address most of the issues but if there are final pieces that we don't agree with, those will be outlined in the guidance document.

(Amanda): Okay. Thank you.

Jennifer Goode: You're welcome.

Coordinator: Question is from (Enrique). Your line is open.

(Enrique): Yes, thank you. So similar to the gas pathway in the context of an inhaler product where you're breathing through a plastic component, it's indirect contact with the lungs. So would you consider that tissue or blood, considering that you know, deep lung would have absorption into the bloodstream.

Jennifer Goode: So my understanding is that we generally consider this to be a tissue contact but we would probably have to double-check with the team that reviews those

devices. So if you wanted to send me an email, I can follow up with you to get a very specific answer.

(Enrique): Thank you.

Coordinator: The next question is from (Rose). Your line is open. (Rose), your line is open.

(Rose): Can you hear me now?

Jennifer Goode: Yes.

(Rose): Okay. Great. Good afternoon. Thank you so much for the presentation. It's been extremely informative and very appreciated.

I have a question on where the agency stands with condoms, if you will.

Jennifer Goode: I'm sorry. You went out a little bit. Can you repeat the question?

(Rose): Yes. Where does the agency stand on latex condoms?

Jennifer Goode: Can you give a more specific question?

((Crosstalk))

Jennifer Goode: …medical devices but I'm not sure what your question is.

(Rose): Yes. What is the process that they have to go through?

Jennifer Goode: So they just have to do a normal submission and address biocompatibility information in the submission. I think if you want more specific information,

you're welcome to email me and I can try to coordinate a reply with the review branch.

Irene Aihie: We'll take our next question.

Coordinator: The next question is from (Miraj Patel). Your line is open.

(Miraj Patel): What are the medical devices intended to do? How are they used for protecting and promoting public health?

Angela Krueger: Hi. This is Angela Krueger. This webinar is focused on biocompatibility and specifically related to issuance of the final guidance. So we're going to focus on answers to questions that are related to the guidance and content of the guidance. That particular question…

(Miraj Patel): Okay.

Angela Krueger: …is quite broad.

(Miraj Patel): So could you please answer what you mean by biocompatibility guidance again? I didn't have the audio. I'm audio disabled. So could you just give me a broad overview of biocompatibility guidance?

Jennifer Goode: So I think that my entire presentation was specific to what's included in the biocompatibility guidance, including a definition. And those slides will be available after this webinar today so that you will be able to see them. There is very little that I said that wasn't also on the slides. And so there's…

(Miraj Patel): Okay. So when I speak with social…

Jennifer Goode: …a definition for biocompatibility.

(Miraj Patel): Okay. When I speak with Social Security Administration on Health and Human Services for example to enroll in hospital insurance and supplemental medical insurance, there is a 24-month waiting period for that, for part A and part B of Medicare.

Does your session fall under part D of Medicare, that extra health or prescriptions area?

Coordinator: I do apologize. Our next question is from (Fred Julio). Your line is open.

(Fred Julio): Does the agency have any updates in regards to accepting in vitro model testing for irritation and sensitization specifically on class one devices that have a duration of less than 24 hours?

I bring this up because our customers constantly bring up the fact that they want to get away from animal testing.

Jennifer Goode: We are willing to consider in vitro alternative tests to some of the traditional tests that use animals. And we are in dialogue with various groups that are interested in using that type of testing. We do ask for some validation information to support those types of tests before we allow their use. And we have not currently reviewed validation information for those two specific tests that you identify.

So if your group is interested in using that type of testing, we would be happy for you to send me an email. We can set up some discussion time to figure out how to move forward.

(Fred Julio): Okay. Thank you.

Coordinator: The next question is from (Anthony Watson). Your line is open.

(Anthony Watson): Hello. My question has to do with the agency's view on whether biocompatibility is based on intended use or likely potential of contact? And I'll be more specific for you. This question has come up in the case of hypodermic needles where in one case it might be in particular case for this use might be for subcutaneous only, but there is the potential possibly of maybe coming into a vessel or something like that.

Jennifer Goode: So I don't actually know how those products are reviewed in the division that has purview of those. So the consideration from a global perspective is that you would think about how it is likely to be used. And so the various biocompatibility endpoint considerations should be considered from that perspective.

Again, if you want to email me I can follow up with the biocompatibility reviewers in the group that tend to look at products like that and find out if they do consider vessel and blood contact as well as subcutaneous contact. But I don't know that off the top of my head.

(Anthony Watson): Thank you.

Coordinator: The next question is from (Josh Sharma). Your line is open.

(Josh Sharma): Yes. My question is about implantable device class three, greater than 30 days. I looked at your Attachment D -- biocompatibility evaluation flow chart -- so my question is if we have a device which is identical and similar to what

is already on the market, according to this main chart, that we need not to do any biocompatibility test. (Unintelligible) if it is the rationale?

Jennifer Goode: So it's true that if you're comparing to your own device and you know all of the information on the formulation and manufacturing, you could potentially make a rationale for why you wouldn't need to repeat testing. And you can do that whether it's an implant device or a short-term use device. The level of information that you might need for an implant device could be slightly different because the actual physical properties of the device could impact the biological response as well as surface properties or geometry.

So the type of information that you might have to provide for an implant could be more extensive in terms of comparing and showing that it's identical.

(Josh Sharma): Okay. In that case, the biocompatibility test could be exempted, correct?

Jennifer Goode: If we agree with the rationale.

(Josh Sharma): Okay. And that information, we could submit it at the time of presenting the PMA or should we do it before PMA submission?

Jennifer Goode: If it's your first time submitting a PMA for a device, this is something that I think would be prudent to talk to us about before the PMA is submitted. If you're comparing to your own product, you still might want to come in with a presubmission to make sure that we agree with your general approach.

We talk in the guidance about how we can't necessarily review an entire rationale, a detailed rationale, in a presubmission. But we have found that use of a presubmission process specifically for this type of approach can be quite helpful.

(Josh Sharma): Thank you very much.

Coordinator: Our next question is from (Diane). Your line is open.

(Diane): Hi. In the guidance document on page 18 it includes a reference to nonclinical laboratory studies being conducted in accordance with 21 CFR part 58.

When you go to part 58, specifically section E, application for research or marketing permit license, this section does not include a reference to premarket clearance.

So on slide 14 of your presentation you are stating that the guidance document is applicable to the 510(k). Can you speak to the conflict between the guidance document and your slide?

Jennifer Goode: So for those who don't know, the regulations that you're referring to are the GLP regulations. The GLP regulations point out that if you're using preclinical testing related to safety in a biological system, then GLP regulations would apply. And so that's the point that we're trying to reiterate here in the guidance, that if you're doing biological assessment for safety, you should be considering the GLP regulations.

I'm not an expert on this specific section E. I don't have that memorized. So I apologize if I'm not directly answering the question you're asking. We do have various regulations for IDE, PMA, and 510(k) program that talk about a need for preclinical assessments and while they may not specifically reference the GLP regulations, this is historically something that we have considered for any type of biological safety assessments including biocompatibility.

And we point out in the guidance document that if a test wasn't done per GLPs, we would consider it as long as you include the appropriate information that explains why the data integrity has been maintained.

(Diane): Okay. So one of the examples that you used in your slide, the biological evaluation of gas paths. This would relate specifically to anesthesia systems which are cleared through the 510(k) process.

So if you were to look at part 58, they have a very long list of different submissions that are applicable, that the non-clinical GLPs are applicable. And they include IDEs. They include everything that's in 514 except the 510(k) reference. They even include the de novo reference. So I just.

Jennifer Goode: So as I previously stated, my understanding of the GLPs is if you're doing a biological assessment that is related to safety, we do have the purview to ask about whether or not GLPs apply. We don't require for 510(k)s that you have to do a GLP study. And so the guidance very specifically explains that if you don't do a GLP study, we do need a little bit of information to understand how the test was done.

So I guess if you need more detailed information than that, I'm happy to follow up with some people who are a bit more expert in the actual nuances of what's in the document. I don't have it in front of me, that particular regulation so I can't speak to very specific aspects of it. But I'm very happy to follow up more on that for you if you think that you need more information.

(Diane): No. I didn't quite understand that from your first response, that the GLPs are recommended for the 510(k). That would explain the difference. So no, you answered it now. Thank you.

Jennifer Goode: Great. Thanks.

Coordinator: And our next question is from (David Millet). Your line is open.

(David Millet): Thank you Jennifer for this presentation today. I have three questions. Is geno - none of them relate to novel materials. Is genotoxicity testing required for all limited duration direct blood contacting devices? Or only those used in extracorporeal circuits?

For genotoxicity testing, is it acceptable to use neat extracts undiluted, prepared under standard conditions described for ISO 10993-12? Or must it be exhaustive extraction?

In what cases is an in vivo genotoxicity test required?

And lastly, could you please comment on the use of material mediated pyrogenicity testing? When is this not required for blood contacting devices?

Thank you.

Jennifer Goode: So I'm going to repeat your question and make sure I've got it right, and the answer. I thought that I heard four questions.

The first question was: do you always need to do gene tox for less than 24-hour direct contact with blood. You do need to assess genotoxicity either through testing or some other type of assessment. And the details of that are in the guidance for new materials and contact with the blood and cardiovascular tissue, if it's never been used before in a medical device application for other devices beside the extracorporeal devices.

For extracorporeal devices, we do ask for the gen tox assessments. And it could be testing or a rationale.

The second question was whether exhaustive extraction was needed for gene tox testing. We do not require that at this point in time. So if you did a normal extract for a gene tox test, that would be acceptable.

The third question you asked for some examples of when in vivo genotoxicity testing would be required. I'm just going to flip open to the guidance on that because I don't have that off the top of my head. So if you can just wait one second on that.

(David Millet): I think I was asking more about the material mediated pyrogenicity in my third question. When would that not be required, the test data?

Jennifer Goode: So as we point out in the guidance, for any devices in contact with blood, you have to address the endpoint in some way. And so you can do a test or you can explain why it's no different from something that you've presented to us before and therefore you think that you don't need to do material mediated pyrogenicity. Or you can compare it to something else that you're aware of on the market. But it's sometimes harder to compare to somebody else's product than your own.

So for all of these end points where we're talking about something in Attachment A, it could be either a test or an assessment. Was there anything else?

(David Millet): For the material mediated pyrogenicity we often do a chemical characterization that involves leachable, extractable testing and we get unknowns as part of that. Is it - and so our interpretation of this guidance is

that if we don't see a known pyrogen in our assessment, is that acceptable to the Agency? Because we always have unknowns and we're not sure whether that means we should always be doing this material mediated pyrogenicity testing or whether our examination of our device, which does not include novel materials, is acceptable with that sort of an assessment.

We look at the leachable extractables, identify what can be identified and consider the risk from that perspective.

Jennifer Goode: So I would say that how you do chemical characterization may impact whether or not that type of data would be sufficient. Unknowns could cause pyrogenicity and so I think that if you have an extractable leachable study and you have very low amounts of unknowns, that might be okay. But that's the kind of thing that we probably would want to have a better understanding of how you did that testing and what levels of unknowns you have.

So when I speak to chemists within the agency and outside the agency, unknowns can usually be identified but it can be a lot of work to identify them. And so we're not saying you always have to do more expensive, more difficult tests. But there are some purists who would indicate that you can always pretty much figure out what an unknown is.

We would not always require that, so the details of your particular case would need to be shared with us in order for us to give you a good advice on that.

(David Millet): Okay. Thank you very much.

Coordinator: And our next question is from (Nancy Sowers). Your line is open.

(Nancy Sowers): Hello. Thank you. This has been an interesting presentation. We are curious here about the very broad scope of the recommendation to consider material-mediated pyrogenicity for many device classes. And it's a much broader class of devices than the agency typically is looking for information on endotoxin-mediated pyrogenicity.

And for us to be able to evaluate whether or not we might need it in a given case would really help to understand what was your thought process in putting out that broad recommendation. So for instance, a, you know, less than 24-hour contact with tissue bone dentin, that's not considered subject to endotoxin-mediated pyrogenicity. But yet you're asking for the evaluations here. Could you please explain?

Jennifer Goode: So our position is that these recommendations for material-mediated pyrogenicity are consistent with our original G95-1 recommendations. But they weren't spelled out specifically in ISO 10993-1. In that actual standard they do talk about material mediated pyrogenicity as a subset of acute systemic toxicity, and if you look at 10993-1 Attachment A, our matrix is very consistent with what's provided in 10993-1.

We also worked very closely with our colleagues on the cleaning and sterilization side to make sure that what we were recommending here for pyrogenicity was consistent with some recent recommendations for bacterial-mediated endotoxin.

And so this is our current policy and it is applied to both.

(Nancy Sowers): Okay, thank you.

Jennifer Goode: Yes.

Coordinator: And our next question is from (Johung Tai). Your line is open.

(Johung Tai): Hi. Thank you very much. This presentation is very informative. So I have a couple questions. The first one is talking about the cytotoxicity testing. So I saw that the cytotoxicity testing, you mentioned the new guidance ask to conduct at 37c for 24 to 72 hours.

But I saw standard testing current just required 24 hours. So my question is when do we need to consider about 24 to 72 hours? In which situation we need to do 72 hours?

Jennifer Goode: So ISO 10993-12 sample preparation does include a 37-degree C 72-hour extract -- which is the sample prep standard. We do ask companies who are manufacturing devices that are used for longer than 24 hours to consider a 72-hour extraction for their cytotoxicity test.

We've talked with many test labs about this. It is possible for the media to be extracted that long in a cytotoxic media that's used for this test. And the proteins in that extract may be depleted slightly over that extraction condition but if there are no material problems, the cells are usually fine.

(Johung Tai): Okay. Thank you. The other query about cytotoxicity testing is in the ISO guidance, they listed the four types of cytotoxicity testing. So such like neutral red uptake, colony formation, MTT-XTT, and in (unintelligible) with that there is three or four cell lines. So is that FDA has specifically looking to one type of testing or one type of line, or it doesn't matter as long as within this recommendation, the method and the cell line be acceptable?

Jennifer Goode: So we do currently recognize ISO 10993-5 I believe in its entirety which includes all these different methods. And what that means is that you can select from those tests and you can use the cell lines that are outlined in the standard. If you use a different cell line, we may ask some questions about that. So that might be good to touch base with us on this. But in general, those methods in 1099-5 are acceptable to us.

(Johung Tai): Okay. Thank you. I have another question about the extraction. It seems that we are doing a lot of the extractions. So I'm concerned about extraction conditions. So first question is about the extraction duration.

In the traditional biocompatibility extraction, the method described in 10993-12 they're talking about four kinds of extraction conditions. And FDA particularly wants to have a high temperature. But is that the specific link to the duration?

For example, if I have one device used for 28 days or 38 days, do you think that 50 degrees C 72 hours is still applicable? Or want to have something other than these traditional conditions?

Jennifer Goode: So for long term use devices, if the solvent, the extract solvent is not going to be compromised by the higher temperatures, it's generally accepted in the biocompatibility community that an extraction condition such as 50 degrees C 72 hours should be representative of what might come out over the longer time frame. And so a 37-degree C 24-hour extract in saline or cottonseed oil would generally not be acceptable for a device that's used for more than 24 hours.

Usually the temperature selection is impacted by the material properties and the transition temperatures of the materials in the device. So if you have a

material that can't withstand those temperatures, then you couldn't use those extraction conditions.

But many device materials can withstand those higher temperatures and it's generally accepted that those higher temperatures will be representative of what might be extracted or leached over time.

(Johung Tai): Okay. Yes. Thank you very much.

Jennifer Goode: You're welcome.

(Johung Tai): Other question about extraction condition is talking about the storage conditions specified in the page 26 that's required to no longer than 24 hours' storage time. This is specifically described in ISO 10993 series regarding the in vivo and in vitro testing.

But it does not, you know, specify -- at least maybe I missed it -- not specify in the chemical analysis. So is that still being required for chemical analysis? Or is it not? Because I contacted a couple testing lab. The common practice they just like extract it and store in the freezing temperature for a short period of time over 24 hours.

Jennifer Goode: So we do recognize that standard which says you can store up to 24 hours and you can freeze for longer if it doesn't affect the materials. So if your medical device has materials that cannot withstand those temperatures, if we know from your device description that the materials may be susceptible, we may ask for some validation that the materials don't change with that storage.

But in general for many medical device materials, those standard storage conditions should be fine. The caveat is that for blood contacting products, if

you're doing an extract, there may be changes to the blood if it's stored prior to use in the extract. So you have to be aware of that.

I think we have a lot of people waiting to ask some questions, so I think if you have more questions perhaps you can send me an email with those and I'll try to get back to you quickly.

Coordinator: And our next question is from (Paul Blackwell). Your line is open.

(Paul Blackwell): Hello. In regards to coded reprocessable medical devices, is it recommended to consider pre and post cleaning impact during cytotoxicity testing for assessment of leftover cleaning residues?

Jennifer Goode: So I actually am not an expert on the reprocessing product. So that's a very good question for you to send to me so I can share with my colleagues. I apologize to you that I don't have an answer to that question.

(Paul Blackwell): Okay. Thank you.

Coordinator: And our next question is from (Tom Kelly). Your line is open.

(Tom Kelly): Yes. I just was curious about your viewpoint on legacy products and biocompatibility. Any continual testing how, that's all I'm looking for. So just getting your thoughts on that.

Woman: One second while we get that answer for you.

(Tom Kelly): Okay.

(Joni Foy): This is Joni Foy from FDA. I think, you know, in regards to the legacy products, we strongly encourage you to provide a rationale as to how your product is analogous and similar to other products that you may already have gotten through the FDA process -- either cleared or approved.

We would like for you to provide a rationale, as Jen has mentioned, and that is included as part of the biocompatibility guidance document.

(Tom Kelly): Okay. Well thank you.

Coordinator: And our next question is from (Thor Rollins). Your line is open.

(Thor Rollins): Thank you. It's always very helpful, Jen. I appreciate it. My question has to do with complement activation. In the new guidance it says that you're recommending assessment of the SC5b-9 fragment activation. And in the past, you've always included the C3A also for the other pathway.

I just wanted to see kind of what was the rationale for just including the SC5b-9.

Jennifer Goode: Sure. We got a lot of comments on the complement activations section with many people submitting to us articles and various rationales for why complement activation testing might not be needed at all.

And so we worked really hard to figure out what - if we needed some testing, would it be acceptable to just do one test instead of the two tests to help minimize the burden to our device submitters? And we spoke with the developer of the complement activation test about the differences between C3a and SC5b-9.

We know from the literature that one of the problems with the C3a fragment is that it can sometimes absorb to the vessel walls in the extraction vessels. And so you may get an undercount.

And so we had been asking for both tests because while SC5b-9 sometimes shows lower levels, it may be harder to discern differences between positive and negative responses just because the total volume of complement is lower, There are less issues with absorption.

And so in talking with the developer of these methods, he was in agreement that because SC5b-9 is further down on the complement activation pathway, it should be sufficient to capture materials that might also activate C3a.

(Thor Rollins): Perfect. I appreciate that. Thank you very much.

Coordinator: Thank you. And before we take our next question, we would like to ask all participants if you ask a question, please limit yourself to one question and one follow up question.

Our next participant is (Delora Conseca). Your line is open.

(Delora Conseca): Hi. I am wondering, a lot of the guidance refers to selecting a test for particles or, you know, considering (unintelligible) of your particles. But there is not specific standards that we know of for medical devices in particle testing. There's only a reference that we noted, the USP 788.

Does the FDA have or provide guidance on particle testing for medical devices? Thank you.

Jennifer Goode: I'm looking up at the ceiling trying to think if I know of any. I actually am not specifically aware of standard numbers that I can tell you right now. I know that there are various standards that can be used to think about particle assessment, and I earlier this week had an email to a colleague asking for those lists, but I haven't gotten that yet.

In general, I think we can say today now that different device groups do have some very specific ways that they would like particles to be considered that may be specific for example to an absorbal device versus a durable device.

So some of this may actually be very particular to a device type. But if you do want to follow up with an email -- I'm sorry I keep saying that -- I can pull together some standards and I can tell you how they might be used in general.

The other piece that I want to say about particulates is that the amount that can be tolerated from a biological response perspective may depend on the chemistry and the size of the particles. And so I'm not aware of any standards that say you can have X amount of a certain size for any medical device and that will be fine. And very often in the device areas that I've worked in, we've said if you developed a program for a particular device where we are worried about particle generation and you can show through either animal testing or clinical testing or clinical use that that product doesn't have a problem and you can maintain for that material that level of particles, that would be acceptable.

If you want to allow an increased level of particles, we would look at that and we would have to have some dialogue with you on whether or not that would be acceptable.

(Delora Conseca): Thank you. Your email then is the very first one on the top of the last slide?

Jennifer Goode: My email is Jennifer.goode@fda.hhs.gov. So it's the middle email.

(Delora Conseca): Okay. Thank you.

Coordinator: And our next question comes from (Ian Miller). Your line is open.

(Ian Miller): Good morning. The question that I have is there a ruling on the modification for genotoxicity testing? Are there still three separates suggested tests that need to be conducted?

Jennifer Goode: So as outlined in the guidance, there are two in vitro assessments that if testing is needed we would recommend. And the third in vivo test is not something that would generally be required. And the guidance talks about when you might need to consider that third test.

(Ian Miller): Okay. Thank you very much.

Coordinator: Our next question comes from (Ben Hornsy). Your line is open.

(Ben Hornsy): Hi yes. I actually already had my question answered. So thank you.

Jennifer Goode: Thanks.

Coordinator: Thank you. The next question is from (Erin Meed). Your line is open.

(Erin Meed): Hi Jen. Thanks for the presentation. I have a clarifying question based on the agency's recommendation to test new components separately for the other materials in the device. Does that mean that the new component or new

material still needs to also be assessed as part of the final finished device? Or is the component level assessment sufficient?

Jennifer Goode: So this is an "it depends" answer. One of the things that we think about when we're looking at component testing is whether there are joining processes that have been assessed. And so if you're making separate components and you're not putting them into the final finished device before you take them apart and test them separately, you may not actually have all of the manufacturing processes incorporated into that component.

And so I think that there are some materials in cases where just doing an assessment of the final finished device would be enough, and some cases where we would say, you know, you have a huge device and this is one piece that's a new material and there's known toxicities for that material. Can you test that separately?

So I think you have to be careful about doing a subcomponent before you've done all the final processing. And then if you're separating components, then you also have to think about how you separate them and whether or not that would impact potentially the biocompatibility. And reasonable rationales would certainly be considered there.

(Erin Meet): Thanks, Jen.

Jennifer Goode: Yes. Sure.

Coordinator: Our next question comes from (Doug). Your line is open.

(Doug): Hi. My question is about if a process changes and what biological effects we need to reconsider. So if the sterilization has changed from say Ebeam to

ethylene oxide, is it appropriate to just consider cytotoxicity and hemolysis, or will all of the biological effects need to be reconsidered?

Jennifer Goode: So hemolysis and cytotoxicity are not informative of the other endpoints. So we would not recommend that just looking at those two endpoints would be sufficient. Depending on what the starting materials are…

(Doug): Yes.

Jennifer Goode: …and what the change is, with a change in sterilization, there could be a drastic impact on the final device if the chemistry changes drastically. For example, you could have different outcomes in a test other than cytotoxicity or hemolysis that wouldn't show up as a change in one of those two tests.

So you don't always need to do testing…

(Doug): Yes.

Jennifer Goode: …but you do need to address all of the endpoints.

(Doug): Okay. And then so if the current product is currently released in the product and has been for years and we're reevaluating our biocompatibility of the product, not for any change but for just a quality assessment, would it be appropriate to leverage the current device that's on the field?

Jennifer Goode: So that could be a part of a rationale. However, it sometimes is difficult to use clinical data to address very specific biocompatibility endpoints. So if we were to accept that kind of rationale, I think that type of dialogue would be helpful to have outside of the submission specifically to make sure that we're all on the same page.

(Doug): Okay.

Jennifer Goode: But we would consider that.

(Doug): Thank you.

Coordinator: The next question comes from (James). Your line is open.

(James): Hi. I just wanted to confirm whether the FDA still considers times zero as a worst case for biocompatibility and would there ever be a situation where the FDA would require an age data for biocompatibility purposes?

Jennifer Goode: So I would say that in general we do accept testing from products at time zero for manufacturing. If we're concerned about aging, we may, for that device type, ask for some other type of information.

So I can give you an example from a device area where I review. We do ask how chemistry changes over time for products such as sealant. And so you wouldn't do biocompatibility at the end of the shelf life, but those products generally have chemistry information for the shelf life. And so those companies would do biocompatibility of time-zero manufactured product and then have other types of information to look at whether or not it changes over time for shelf life.

(James): Okay. Thank you.

Coordinator: Next question comes from (Phillip Gramble). Your line is open.

(Phillip Gramble): Hi. Thank you for taking my question. Do you have a recommended pathway when one of the listed biocompatibility tests is I would say not compatible with the product? And the specific example that I have is resorbable material. One of the byproducts is lactic acid, which will never give an acceptable cytotoxicity result. But through all of the other biocompatibility tests is acceptable. Thank you.

Jennifer Goode: So for absorbables we know that sometimes the change in absorption could affect endpoints such as cytotoxicity. We generally ask that cytotoxicity be conducted anyway. For some of these products where we're expecting a cytotoxic response, we talk about this in the guidance, we sometimes will ask for dilution studies so that you can tell at what point the cytotoxicity goes down. And then if you make a change in the future, often companies will use that test to say see it's still toxic at the same, you know, dilution.

But there are also sometimes some sample prep approaches for absorbables that might be acceptable on a case by case basis and we do generally look at products where cytotoxicities are expected and say yes, we understand.

We don't necessarily think that you should not do a test just because you expect it will be toxic because sometimes differences in manufacturing preparation could impact the level of cytotoxicity seen. And so if there's a justification for not needing a test at all, that's the justification. But if that endpoint needs to be assessed by testing, we would expect there to be a modified test perhaps or the test as described in the standards.

And we do know that for absorbable products, that sometimes sample preparation can be helpful to this.

(Phillip Gramble): Thank you.

Coordinator: Our next question is from (Christine Ni). Your line is open.

(Christine Ni): Hi. My question is about direct and indirect contact. How would you categorize an accessory which is used to prep an implant?

Jennifer Goode: So for an accessory that's used to prep the implant, the accessory itself would have indirect contact because materials from that prep accessory could end up on the implanted device.

(Christine Ni): Yes.

Jennifer Goode: And so you would consider the implant category for that indirect contact with the accessory.

(Christine Ni): Okay. Thank you.

Coordinator: The next question comes from (Bill). Your line is open.

(Bill): Hi. As a plastic compound raw material supplier, we've been testing things to USP 88, Class VI. Is there any reason to switch over to ISO 10993 to make life easier for our customers?

Jennifer Goode: So we do have material suppliers who work with their customers to provide device master files to the FDA. And if those device categories that the material is used in require sometimes endpoint information such as hemocompatibility, which is not included in the USP class six testing, then an ISO 10993 approach could be helpful to that.

One of the issues that we do have with device master files is that if there's not a lot of good information on manufacturing and if the materials themselves are complex, it's sometimes helpful for medical device manufacturers if the master file includes some information on acceptable manufacturing conditions over which that biocompatibility information might apply.

And so there is an attachment in our guidance document -- Attachment B -- which includes some recommendations for what could be included in a device master file that could be helpful to a medical device manufacturer if a supplier were willing to submit that.

(Bill): Okay. Thank you very much.

Jennifer Goode: You're welcome.

Coordinator: Thank you. The next question is from (Jeff). Your line is open.

(Jeff): Hi. Thanks for having this webinar. I notice the ISO guidance on material mediated pyrogenicity hasn't been updated in some time. And it's actually surprisingly brief. I'm wondering if FDA has any additional information or guidance on clinically relevant material mediated pyrogens that are of interest to the agency.

Jennifer Goode: I don't actually have any of that information. I know that there is an ISO group that's looking at pyrogenicity endpoints. They've been working on a document for some time. It was recently balloted and it should be coming out soon. But I don't have any specific information on types of pyrogens that we would be concerned with.

Coordinator: The next question is from (Anya Ramesh). Your line is open.

(Anya Ramesh): Thank you for your interesting presentation. I have one question. You said in your guidance documents that GLP certification is needed for in vitro and in vivo studies. What about chemical testing? Do you accept ISO 17025?

Jennifer Goode: I don't know what ISO 17025 is. But in general, because the chemical testing is not using a biological system we don't require GLPs for that.

(Enya Ramesh): Yes. Okay. Thank you.

Jennifer Goode: You're welcome.

Coordinator: The next question is from (Catherine). Your line is open. (Catherine) can you please check your mute button? Your line is open.

The next question is from (Frances). Your line is open.

(Frances): Hi. (Unintelligible) know if FDA recognize two performance study looking at visual observation of any thrombus left behind on the short term, like a catheter or guide wire after being evaluated in large animal study.

Jennifer Goode: So it was a little difficult to hear you (Frances) but I think your question was whether we would accept an in vitro assessment of thrombogenicity instead of an in vivo assessment of thrombogenicity for short term use devices in contact with blood, such as catheters or guide wires. Is that correct?

(Frances): No. I'm interested in the use of acute performance large animal studies evaluating the (unintelligible), evaluating the performance guide wire or catheter.

Jennifer Goode: Okay. So yes, we have accepted some acute data from large animal studies for these short term use devices. We do include some information on that in the guidance document in terms of how to think about doing those assessments and we do often have dialogue between our animal study reviewers and companies who are developing the tests so that before the large animal studies are conducted, we check to make sure we agree with how those types of end points are being assessed.

(Frances): Okay. Thank you.

Coordinator: The next question is from (Lolita). Your line is open. (Lolita) can you please check your mute button? Your line is open.

Our next question is from (Danny). Your line is open.

(Danny): Hello. Under Attachment A, for example FDA has historically considered devices used in drain fluids as Foley catheter as externally communicating rather than surface. When that's incongruent with ISO 10993 Part One 2009, what's the explanation for that statement regarding Foley catheters?

Jennifer Goode: Just a second. I'm finding the statement because I don't have that memorized. Sorry.

Sorry. I was having trouble finding it. Okay. So yes, so I think that what we're seeing here is a discussion of the fact that since before G95-1 was written, the branch decided that that's how they were going to review those and those were the assessments that they were going to ask for.

And so this was in the early 90s. And we wanted to make sure people understood that we were going to assess things this way so that they wouldn't be confused if they were looking at 10993-1 instead of the FDA guidance documents.

I don't think that the people who originally made that decision actually work at the FDA anymore and so I can't necessarily give you a specific technical reason for it. There is one colleague of mine who I may be able to ask. So again I apologize but if you want to email me, I know who I can ask and if they know the answer, I'm happy to share it with you.

(Danny): Okay. Thank you.

Coordinator: Thank you. And our next question comes from (John). Your line is open.

(John): Hello. This is a great discussion. I just wanted to find out what information or resources are available for materials that are used in devices that we can use for biocompatibility risks? And if there are any data or FDA sources available to the public that can be used in submissions to possibly to eliminate the need of testing. And that's with as long as our manufacturing processes are considered not imparting contaminants.

And I have another question. I was wondering if you could just basically describe the difference between the X's and the O's because I don't understand the difference between those. Thank you.

Jennifer Goode: Okay. I'm going to take your second question first because that's an easier one for me to answer. And I'll try to explain it with a copy of the slide up for everyone to see if you're looking at the slides. And I'm…

(John): Okay.

Jennifer Goode: …going - I don't want to go too fast. So if you get dizzy close your eyes for a second. I just went past it. Okay. So in this table, which it comes from the subset from our guidance document attachment A, you will see X's. Those X's mean that ISO 10993-1 also agrees that this endpoint should be assessed.

Since G95-1 we've always looked at whatever the version is of 10993 and said are there endpoints that we ask for that ISO also does not ask for. So an O means that since 1995, we've also asked that people consider these O's. So we have not been in 100% agreement with ISO. Since 1995 ISO has changed over time. So sometimes we get more X's and fewer O's. But the O's basically say it's not called out in Annex A of 10993-1 but we want to make sure people understand that for FDA they also have to consider these endpoints.

Now the good news is that before we published this guidance document, we met with the ISO experts who are working on a revision to 10993-1 and we said we have all of these O's. Do you guys agree that people should at least talk about these things in their submissions for these various categories? And they said that seems reasonable. So we're hoping that the next revision to 10993-1 will include the same endpoints that we're asking for here in this guidance.

So because of publication differences and world expert discussions that may or may not actually happen, but we're hopeful that it might.

So right now what happens is you have a published 10993-1 in 2009 and they identify everything that's an X. And in our guidance we say don't forget, we also have some additional endpoints we want you to consider and those are the O's. Does that help?

(John): Yes. Thank you very much.

Jennifer Goode: Okay. And then your first question was whether or not FDA has data sources that could be useful to companies. And unfortunately the way FDA works, when people submit to us it is proprietary and we can't share that back with the external world. And so we don't have a specific data source that could be used by manufacturer to say because I'm using this process, I therefore don't need to worry about biocompatibility.

What we do encourage people to think about is how their own products compare to things they've done before. And we have some companies that are very successful at providing us with rationales. Depending on what the change is, different levels of information might be needed. It might be sufficient to provide a descriptive explanation.

In some cases, manufacturing residuals and impurities are unknown and they're difficult to track down. Depending on your device risk and the materials you're making something out of, we may ask for more information if it's a higher risk device and a material that has more potential for impurities or manufacturing residuals.

So we don't necessarily want a 2000-page rationale with all your manufacturing processes because that will be hard for us to review in a timely fashion and provide you with feedback. However, we do ask you to consider how you're making your device and if you have contract manufacturers who are making your device and they want to submit a master file to us so that some of their proprietary information can be held by us, we don't release that information. We just use that in the context of a review. That's one avenue that some companies successfully use.

(John): Okay. Thank you very much.

Jennifer Goode: You're welcome.

Coordinator: Thank you. Our next question comes from (Ruby Rodriquez). Your line is open.

(Ruby Rodriquez): Hi. We had a question in regard to an FDA approved material and if this would fall under the category of if biocompatibility would not be need to be tested again.

Jennifer Goode: So as explained in the guidance document, FDA does not approve materials. We clear or approve medical devices. And so as explained in the guidance, our position is that you could have a starting material from one supplier that's absolutely fine. You could get a starting material from another supplier that could have some residuals or unknowns to you that are toxic.

You then could do manufacturing and at one manufacturing site something might not be completed properly and there might be residuals left over that are not fine. At another manufacturing site, it might be fine.

And so it's not sufficient for medical device application to say I use a material with a long history of safe use. There is no such thing as an FDA approved material for medical devices. And so we do expect people to explain why they think their materials and their medical device in this final finished form will not cause a biocompatibility issue if they do not want to do testing.

(Ruby Rodriquez): Okay. Thank you.

Jennifer Goode: You're welcome.

Coordinator: And our next question comes from (Deborah Webster). Your line is open.

(Deborah Webster): Yes, hi. Thank you for this great discussion and informative presentation. I have a question about the type of biocompatibility testing that would be required for devices that are made out of human or animal tissue -- in particular like the extracellular matrix devices and hyaluronic acid.

The type of extraction testing - or would there need to be any kind of extraction testing done on these for cytotoxicity and genotoxicity? It doesn't seem like it would be plausible to do.

Jennifer Goode: So that type of product is actually out of the scope of this guidance document. It's not an area of expertise of mine. But I'm very happy to follow up with some of my colleagues to answer any specific questions about that if you'd like to email me. And I'm going to go to my email slide again.

(Deborah Webster): Okay. You know. I already have that lined up.

Jennifer Goode: Okay.

(Deborah Webster): What type of biocompatibility testing is mostly for things that are not of biological origin then?

Jennifer Goode: Biocompatibility needs to be addressed for any medical device application…

(Deborah Webster): Right.

((Crosstalk))

Jennifer Goode: …whether or not it's of biological origin or not. And I know that the groups that review devices made of biological origin do ask for biocompatibility information in the submissions if it's not provided. I just can't give you any details in terms of testing or extraction because…

(Deborah Webster): All right. Thank you.

Jennifer Goode: …it's not my area of expertise.

(Deborah Webster): Appreciate that. I'll send you a separate email then.

Jennifer Goode: Wonderful. Thank you.

Coordinator: Our next question comes from (Ian Miller). Your line is open.

(Ian Miller): Hello. Thank you for this wonderful presentation. I had a question regarding animal studies of implantable devices -- specifically we have a class two medical device that we have previously tested and implanted in large animals. But would it be possible if we could show efficacy when conducting the animal study in a smaller animal, would that be acceptable to FDA as long as we properly justified it?

Jennifer Goode: So whenever you decide to use a model different from what you submitted to us previously, we do recommend that you talk with the review branch to make sure that they're in agreement…

(Ian Miller): Okay.

Jennifer Goode: …with the model that you're choosing. In general, our medical device industry tends to use similar types of models for specific devices and if you're going to try and use something different from what your company or companies of similar devices have used in the past, it's really a good idea to talk with the animal study reviewers to make sure they're in agreement that how you've designed that study in that particular model makes sense.

(Ian Miller): Okay. Great. Thank you so much.

Jennifer Goode: You're welcome.

Coordinator: And our next question comes from (Avi). Your line is open. (Avi) please check your mute button. Your line is open.

(Avi): I don't have any additional question. My question was answered in a different question. So thank you so much.

Coordinator: Thank you. And our last question comes from (Michael Nilo). Your line is open.

(Michael Nilo): Hi Jen. Thanks for the presentation today. I do have a question. You brought it up earlier and the person asking actually had a different question.

But what is the current FDA thinking for in vitro thrombogenicity testing versus the in vivo method?

Jennifer Goode: So we also would consider in vitro thrombogenicity approach for various medical devices instead of in vivo thrombogenicity testing, which we've asked for in the past.

The guidance provides a lot of detail on whether a static with just minor agitation but non-clinical flow testing would be acceptable -- for example, for something that's just a material change -- versus a dynamic flow loop. When these types of approaches are taken, we do -- especially for the dynamic flow loop -- ask for some dialogue prior to doing the testing. We do ask for a bit of validation information to confirm that how the testing is done, we can understand and interpret the data.

Sometimes it's difficult to understand the clinical relevance of that testing. And so those types of approaches are something we're very interested in. But we don't necessarily want to see it for the first time in an application because unfortunately, that sometimes creates some questions and we'd rather you guys do testing once and we say that's great, thanks. Because we know what you're doing and we understand it.

(Michael Nilo): Thanks. That makes sense.

Coordinator: Last question is from (Paul). Your line is open.

(Paul): Hi Jennifer. Thank you for the presentation. The question is related to extract and pH. For extracts that fall out of the pH range of 2 to 11.5 -- particularly for an intracutaneous acute toxicity or sensitization studies -- is that testing still required? And would pH adjustment of the extracts be acceptable?

Jennifer Goode: So there are some statements in some of the ISO standards on sensitization, I think, and acute toxicity, that say if you have pH outside those ranges, you should not be doing the testing in the animals because of animal safety concerns. But if you are doing an extract and you get that kind of change and therefore you decide not to do a test, this is a good topic to be discussing with

your review branch to make sure they're in agreement that you don't need any assessment.

Sometimes if a biological test can't be done, and it makes sense based on the materials that you're investigating, we're willing to accept that approach. But if you get that pH change and it's not expected -- for example, if you're using a polypropylene, which is the material used for cell culture dishes and you wouldn't expect that exaggerated pH change -- then we would wonder what's going on with your materials. And more investigation might be needed.

(Paul): Okay. Thank you.

Coordinator: Thank you. And I will now turn the call back over our host for today, Ms. Irene Aihie.

Irene Aihie: Thank you. This is Irene Aihie. We appreciate your participation and thoughtful questions. Today's presentation and transcript will be made available on the CDRH learn web page at www.fda.gov/training/cdrhlearn by Friday, July 29.

If you have any additional questions or comments about the final guidance, please use the contact information provided at the end of the slide presentation.

As always, we appreciate your feedback. Again, thank you for participating and this concludes today's webinar.

Coordinator: Thank you. All parties may disconnect.

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