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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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PUBLIC WORKSHOP - SPINAL DEVICE PREMARKET REVIEW

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M E E T I N G

(8:00 a.m.)

DR. PEAT: Good morning to all and welcome to the Spinal Device Premarket Review Workshop. My name is Captain Raquel Peat, and I am the director for the Office of Health Technology 6, Office of Orthopedic Devices within the Office of Product Evaluation and Quality here at CDRH.

I am really excited to have all of you participate in today's event. Not only is it the first workshop of this type within our office, it is the first virtual format event that we're hosting at this unprecedented time during our response to COVID-19 pandemic. Over 400 persons have registered for today's event, and we're so glad that there are so many of you interested in spinal device premarket review.

This workshop, like other external initiatives, enhances my vision of OHT6 to serve as the world leader in science and regulation of orthopedic medical devices all while supporting FDA's mission. Any leader will tell you that having a vision does not happen without key individuals operationalizing and implementing said vision. Of the many who are participating in this workshop, I want to extend special thanks to Dr. Ronald Jean, Director for the Division of Spinal Devices, and Lieutenant Commander Ogoegbunam, Regulatory Health Project Manager, who both have been instrumental in leading this workshop; staff in OHT6 and other areas of FDA; presenters and group discussion members who are contributing to the implementation of this workshop; and, of course, you, our participants.

So, what are we planning to cover today? Our main objective is to help you, whether you are a patient, doctor, regulatory affairs specialist or payer, better understand how FDA reviews spinal devices under the premarket notification or 510(k) program. In sharing information with all stakeholders, we hope to better improve submission quality

and promote efficient review of orthopedic premarket applications. To do this, we plan on providing you with an overview, as well as useful tips on the major sections of a 510(k) submission. As you can see from the agenda, this spans from the eCopy phase when you're submitting a 510(k) for review, starting from the contents within a device description, identification of a target treatment population for your device through the indications for use statement, all the way to the specifics of performance testing that are evaluated. So, we include biocompatibility, sterility, and mechanical testing.

To have a fair and balanced approach, we also have invited medical device industry professionals to share their perspectives on the 510(k) program during three industry group sessions scheduled throughout the day. Note that although this workshop will focus on spinal 510(k) premarket submission, the information provided can be utilized across all areas of orthopedic medical device portfolio and the submittal of a 510(k) submission. Please note that this is the first of a series of application review workshops that will be hosted by OHT6.

We want to engage with you in the audience, albeit virtually, throughout the day, and to that end, we have included three online audience participation surveys in our agenda.

We also have two dedicated question and answer sessions, one in the morning and another in the afternoon. As such, we have developed a mailbox for you to send questions to called OHT6-Feedback@fda.hhs.gov. This mailbox will be continuously monitored by subject matter experts in our office, and selected questions will be posed within each question and answer session. For questions that are not answered during this workshop, we have every intention of addressing these questions after the conclusion of this event, so please remember this e-mail address, OHT6-Feedback@fda.hhs.gov, or take a moment to write this mailbox address down. The FDA studio will equally post this e-mail address on

your screen throughout the day as a gentle reminder.

In closing, I wanted to introduce our MC for the day who is none other than Sharon Starowicz. Sharon is a regulatory consultant and most recently served as the Director of Regulatory Policy Innovation, Global Orthopaedics, for Johnson & Johnson, where she was responsible for providing strategic regulatory guidance and expertise that impact the medical device industry. Sharon has over 30 years of regulatory affairs experience, specializing in Class I, II, and III orthopedic devices, served as a president of the Orthopedic Surgical Manufacturers Association, and before her illustrious career in industry, she began her medical device regulatory career here at FDA.

It gives me great pleasure that Sharon has agreed to serve as the MC for our Spinal Device Premarket Review Workshop. And I will now turn over to our MC to facilitate the remainder of the day. I hope you enjoy the day as we have an exciting agenda planned for you. Thank you.

MS. STAROWICZ: Good morning, everyone, and thank you so much for that nice introduction, Captain Peat. I am very honored to be part of this informative day that you and your staff have designed for us, and I know we have a lot to cover today, so let's go ahead and jump in and get started.

I'd like to introduce our first presenter, who is Dr. Zane Wyatt. Zane received his Ph.D. from the University of Maryland in material science and engineering. Zane has been with CDRH for 8 years, and he currently works as a premarket software tool developer and policy analyst for CDRH. But prior to that, he spent his first 6 years at the Agency as a lead reviewer in the Office of Orthopedic Devices. So Zane will kick us off today with a presentation on how to avoid an eCopy Hold and talk a little bit about the eSTAR program.

So, Zane, the floor is all yours.

DR. WYATT: Greetings. My name is Dr. Zane Wyatt, and I'm a premarket tools and

templates developer and policy analyst with the Office of Regulatory Programs. My talk today is going to first be about the eCopy Hold program and how best to navigate avoiding an eCopy Hold on your premarket submission. As a center, we are moving towards a more digital ecosystem for the intake, processing, and review of premarket submissions. A key part of this is ensuring that the submissions we receive are easily navigated and read by the frontline review staff. The eCopy program is essential to this effort as it ensures the digital submission files we receive are organized and easily processed for information.

Looking towards the future, our goal is to begin to intake and process fully digital submissions instead of readable PDF files. This can be currently done with a software package called eSubmitter. However, this software package presents many hurdles to achieving the goal of a dynamic, responsive, and flexible digital submission tool. Therefore, as the eSubmitter software package is going to be retired in the near future as we transition into a more digital center, the majority of the rest of my talk is going to cover the upcoming eSTAR electronic submission template. Not only is this a current way to build a submission package that will bypass the current eCopy Hold program, but this will also be the future for submitting true electronic submissions digitally to the FDA.

Here briefly, to give you a sense of the ordering for this talk, we will first cover the three tenets of an eCopy, what it is, how to make one, and what the most common reasons for rejection are. Following that, we unfortunately do not have enough time for a full demonstration of eSTAR's capability or functionality, so I will briefly instead go over the basics of the XML-based PDF software package and its capabilities and then wrap up with both the Center's and industry's next steps to make this transition to digital submissions more successful.

The guidance document for eCopies was most recently updated in April of this year. In this guidance document, the Center discusses the important distinction between eCopy

and an electronic submission. An eCopy is just essentially a digital version of a traditional premarket submission. That is to say, a copy of that submission that resides on a CD, a DVD, or a flash drive. It contains no embedded data, no dynamic functionality, and the reviewer interacts with it much as they would a paper document. Even in the future, as we transition to electronic submissions, there will be a need for non-applicable submission types to abide by the eCopy rules. These rules are a set of technical standards that ensure the version of the submission the Center receives is readable, understandable, easily navigated, and ideally digitally searchable using tools such as OCR or object recognition. If you fail to abide by these technical standards and rules, you will be placed on eCopy Hold, and the review clock on your submission will reset.

The eCopy Hold guidance document, referenced on the previous slide, goes into great detail regarding the technical standards that have been instituted for eCopies. But I'm going to use this slide to highlight the most important ones.

Firstly, do not use security settings or password protection of any kind on any component of the submission package. All of your interactions with the Center are confidential and protected. Adding additional layers of protection only complicates a reviewer's job.

Secondly, you must abide by a very specific naming convention of your files in your submission.

Thirdly, the total file size of a PDF submission must be less than 50 megabytes. Please note that while this includes test report appendices and attachments, it does not include the miscellaneous folder or the stats folder. Therefore, the total size of the entire package must be less than 1 gigabyte. The current size requirements are in place due to our current loading program for in-taking submissions into our internal database. One advantage of the upcoming eSTAR is that this size restriction no longer applies.

Once you have constructed your submission, we highly advise you to run it through our publicly available validation tool. There is no reason today why you should receive an eCopy Hold letter other than if you do not know about this tool. You can upload your submission package to the validation module, and it will process it through all of the eCopy technical standards and make sure your submission passes. Please note, however, that using this validation module does not send the submission to the Center for review. It is only a way to check that your submission meets all of the technical standards of an eCopy.

As I alluded to before, there exists two possible ways to bypass needing to construct your own submission: eSubmitter and the upcoming eSTAR. Both electronic submission packages have built-in eCopy validation. The Center does not yet have an electronic submission portal, so no matter how you decide to construct your submission, keep in mind you will need to still mail it to us for now. Luckily for everyone, our digital transformation initiative will soon change that.

So what are the common pitfalls that currently plague submission construction? Well, it comes down to not really fully understanding or reading the guidance document. Always name your files in your submission according to the defined naming convention. Do not submit file types we cannot read; do not use third-party conversion tools to make your PDFs, as they oftentimes make associated hidden folders; and lastly, use the correct folder hierarchy for your submission. It's pretty basic stuff and nine times out of 10 will always help you avoid the eCopy Hold.

Even still, we do realize that almost 7 percent of current premarket submissions do get placed on eCopy Hold, so there's still a deficiency out there. Hopefully, this deficiency can be solved by the upcoming eSTAR tool.

With our eCopy discussion out of the way, what we really want to get into today is what is coming next. A group of ex-lead reviewers, not external contractors, has been

spending the last couple of years building a totally free, dynamic, adaptive XML-based fillable sponsor submission template for premarket reviews. It has officially launched and, after extensive testing by the Center, has been selected as the future of electronic submissions to the Center. Using the International Medical Device Regulators Forum ToC documents, we have coded and built a sponsor submission form that mirrors the current lead reviewer smart templates for review of premarket 510(k)s. eCopy requirements no longer apply, as the validation is built in. And the best part of this is that a document is open sourced and XML based, so sponsors can build their own APIs to communicate with the template in adaptive form to their existing internal submission building processes.

In addition to mirroring the current smart templates that reviewers are using to assess your submissions, eSTAR contains user guides, integrated databases of standards and guidances, built-in Center policy, procode-specific automation, and many other features all into a single package that will effortlessly guide you through building a comprehensive medical device submission.

In addition, no special software is required of the applicant; it works on any platform, including mobile devices. It will be fully integrated into the future electronic submission portal. And the best benefit of all is that it was built and designed by ex-lead reviewers. No contractors were involved in this, so eSTAR can be expected to be updated often and updated to respond to Center-level policy changes both adaptively and quickly. And also, it can easily be added to or modified based off of real-world use and feedback.

Deployment of eSTAR has already begun. We began a non-IBD 510(k) pilot in February of this year with nine sponsors. That pilot was extremely successful, and we are expanding it to additional sponsors and additional content types this summer. That being said, you do not have to be enrolled in the pilot to use eSTAR. There are instructions on how to make your eSTAR eCopy compliant. Just know that if you are not in the pilot, you

will still receive an RTA review and need to abide by all normal review timelines. But if you want to test drive the template on a real live submission, we cannot, and we especially will not prevent you.

In response to the first pilot, and just ahead of our upcoming summer pilot, we were able to make eSTAR usable for de novo submissions in addition to non-IBD and IBD 510(k)s. As well, we were able to make it 100 percent 508 compliant with user-assisted technology based on lessons learned from the pilot. Also, due to the XML backbone of the tool, the data within eSTAR can now be imported and exported by external tools.

Lastly, and probably most importantly, the tool has been even further harmonized with IMDRF's ToC. This means, for the international companies in the audience, that this tool already abides by the standards, rules, verbiage, terminology, and organization schemas of the other agreed-upon international medical device submission formats. So, whether you're submitting to Health Canada or the FDA, you can use one form.

Coming up this fall and into next year, our plans are to expand eSTAR with a PMA module and then develop a third pre-eSTAR for premarketing submission file types. Now, you may wonder, third? Well, actually, due to the current requirements of the device area, the marketing submission eSTAR is split into two separate ones: a non-IBD and an IBD version.

Therefore, down the road, we will have a pre-eSTAR for all premarketing submission reviews and feedback. This will cover Q-Subs, IDEs, 513(g)s, and all for both IBD and non-IBD devices. This actually, once again, mirrors the reviewers' smart templates. The lead reviewer smart templates for IDEs, Q-Subs, and 513(g)s include both IBD and non-IBD devices, whereas the marketing submissions are broken out.

Then you will have, in the future, the marketing submission eSTAR for 510(k)s, de novo, and PMA where there will be one for IBD devices and one for non-IBD devices, and

this is also mirroring how things are done for lead reviewers with their smart templates.

Thank you very much for having me speak today. It was a pleasure. Feel free to reach out with comments, questions, feedback. We have a publicly available mailbox found on this slide, as well as you can see the links for both additional information on the eSTAR pilots as well as a direct link to the eSTAR tool itself, so you can download and try it out yourself. And this concludes my presentation.

Thanks again, and have a wonderful rest of your day. We are always available to take any questions you may have.

MS. STAROWICZ: Thank you so much, Zane, for sharing this important information and some exciting things in the works for manufacturers in the future.

At this point, it's my pleasure to introduce our next speaker, who is Brittany Ferrell. Brittany will be speaking on some important considerations on the RTA process, and I know that's an area that we're all interested in. Brittany has obtained her Bachelor of Science degree from Virginia Tech. Go Hokies. She's a lead reviewer in the Extracolumnar Spinal Devices Team, and Brittany's been with the FDA for 11 years.

Brittany, it's my pleasure to turn the podium over to you.

MS. FERRELL: Good morning. My name is Brittany Ferrell, and I'm a lead reviewer in the Extracolumnar Spinal Devices Team of the Division of Spinal Devices within OHT6, Office of Orthopedic Devices.

Today I will be presenting on the "510(k) Refuse-to-Accept checklist: Why is my submission not good enough?" Specifically, I'll be presenting on the best practices to ensure your submission will be accepted during the RTA phase of the review process.

The purpose of the RTA checklist is to assess whether a submission is administratively complete and includes all information necessary for FDA to conduct a substantive review and to reach a determination regarding substantial equivalence. It is an

efficient use of reviewer resources because it ensures a complete submission prior to a substantive review, which helps reduce the number of review cycles and total time to a final decision. Additionally, the RTA checklist is a tool to understand key components of a complete submission. It is not intended to evaluate the accuracy of the content or rationale provided in a 510(k) submission. The Refuse-to-Accept policy for 510(k) guidance can be found at the provided link.

The overview of the 510(k) RTA process for traditional, special, and abbreviated 510(k) submissions is presented in this flowchart. Once the 510(k) submission is received, it is checked for a paid user fee and a validated eCopy. If these are not provided, the submission will be placed on eCopy or user fee hold. If the user fee and eCopy are accepted, then the RTA review and FDA clock begins. The reviewers have 15 days to determine if the submission is administratively complete.

If the 510(k) submission is determined to be complete and therefore accepted for a substantive review, an e-mail correspondence stating this will be sent. If the 510(k) submission is determined to be incomplete and the reviewer is unable to obtain this information through interactive review, the submission will be placed on an RTA hold, and an e-mail correspondence with the Refuse-to-Accept decision will be sent. It will include an attachment of the RTA checklist that highlights the elements identified as missing or inconsistent. At this time, the FDA clock stops and will reset to Day Zero when RTA response is received.

If an RTA decision is not made within 15 days, the 510(k) submission will be automatically accepted for a substantive review. There are an unlimited number of RTA cycles; however, our goal is to accept a completed 510(k) submission in as short a time as possible. Our best practice to follow that could lead to an accepted submission would be to fill out the RTA checklist. It is highly recommended that submitters complete and submit

acceptance checklists with their submissions that identify the location of supporting information for each RTA element. A completed checklist becomes a reference document where a reviewer can verify items are present in case the reviewer is unable to locate them. The Refuse-to-Accept checklist can be found in the Refuse-to-Accept policy for 510(k) guidance.

The most commonly missed item in the administrative section is number 8, identifying prior submissions for the subject device. To meet this criterion, we suggest that you specifically state that there are no prior submissions for the subject device, or reference prior submissions by file number for the subject device and state where in the submission all previous deficiencies or feedback have been addressed.

Prior submissions refer to submissions where FDA provided feedback related to the data or information needed to support a substantial equivalent, or SE, decision. Prior submissions can be Q-Submissions; investigational device exemption, or IDE, applications; prior not-substantially-equivalent, NSE, decisions; or prior 510(k)s that were deleted or withdrawn. When addressing prior submissions, we recommend providing a written response addressing each deficiency or feedback element.

To complete the device description section, we suggest that you provide a written device description and images of all subject components and/or modifications. If we cannot understand the device design, especially if it includes unique features, then there is a higher likelihood that your submission will not be accepted.

We highly recommend that a clear description of all design features, for example, expandable and/or complex mechanisms, unique interfaces, and any differences between the subject and previously cleared technological features be clearly explained in the device description; complete dimensioned engineering drawings, which should include all dimensions needed to recreate the device; and an all-inclusive list of components for both

subject and any previously cleared devices. The previously cleared devices should reference the 510(k) number they were cleared under.

The substantial equivalence section requires that the submission identify a predicate device and compare its indications for use and technological features, for example, design features and dimensions. This can be accomplished by providing a device comparison table which should include these mentioned items. Additionally, the identified primary predicate should be consistent throughout the submission in regards to the 510(k) number and the name of the device.

The labeling section requests that an outer package label, instructions for use or package insert and surgical technique manual be included in the submission. Sometimes one or more of these items are not included in a submission because the addition or modification may not change the labeling. However, these documents are still needed for a 510(k) submission to be considered complete. Additionally, indications for use in the labeling should be identical to the indications for use form in the 510(k) summary.

Please specify your device as sterile and/or non-sterile. If your device is sterile, please provide the sterilization method including dose for radiation; a description of the method to validate the sterilization parameters, for example, a full citation of an FDA-recognized standard; the sterility assurance level, or SAL; a description of the packaging; specify the shelf life, expiration date, and specify the methods used to establish packaging and device performance will maintain the sterile barrier for the entire shelf life.

For non-sterile devices, please provide the cleaning/disinfection method which can be included in the labeling, sterilization parameters, state shelf life is not applicable, and provide a statement of why performance data is not needed to maintain the device performance.

To satisfy the biocompatibility criterion, please specify the materials of a subject

device and standards to which they comply. Also, please provide a rationale for why biocompatibility testing may not be needed in regards to materials and manufacturing processes. This rationale can be as simple as stating that the device materials and manufacturing processes are identical to one's own predicate device. When stating this, please remember to provide the 510(k) number of the predicate. Additionally, if there are any changes to the biocompatibility, it is helpful to highlight these changes. The biocompatibility guidance for medical devices can be found at the provided link in the slide.

To satisfy the performance data criterion, both a summary of the test report and full test reports should be provided. The summary should identify the test performed, including standards, the worst-case construct, and rationale for the chosen worst-case components, methodology, summary of results, and discussion of the conclusions drawn from the test results. Complete test reports should identify the test performed, including standards, the worst-case construct components, methodology, and any deviations from the standard, full result tables, images of test setups, images of failure modes, graphs of loading curves, and conclusions drawn from the test results. If any section does not apply to the subject system, for example, electrical or software, please note this in the submission.

The same requirements specified in the administrative device description and substantial equivalence section of the traditional 510(k) RTA checklist are still applicable for the special 510(k) RTA checklist. The special 510(k) RTA checklist also requests a design control activity summary that should include a risk analysis table and a signed declaration of conformity.

The risk analysis table should identify all device modifications and risks associated with the device modifications, specify verification activities performed to address the risks, the acceptance criteria used to validate these risks, and results of the verification activities.

The declaration of conformity should include a statement noting all verification and

validation activities were performed, and the results met acceptance criteria in a statement that the submitter complied to design control procedures specified in 21 C.F.R. 820.30.

Additionally, the labeling section requests that all changes made to the labeling should be redlined or highlighted, or a statement that specifies no changes were made to the labeling should be included.

Our Refuse-to-Accept checklist also includes a helpful tool known as the RTA Addendum. The RTA Addendum is an attachment to the RTA checklist that alerts the sponsor of observations made during the initial RTA review. An observation is an issue identified during the administrative review that does not determine the RTA acceptability of a submission but would result in a deficiency during the substantive review. The RTA Addendum provides an opportunity to address issues interactively during the substantive review. Please note, the RTA Addendum is not a substantive review of submission, it does not take the place of an additional information hold, is not an official ask for additional information or a delay of the RTA review or decision.

The RTA checklist will highlight if an RTA Addendum is attached, and it can be found on the upper left panel under the paper clip icon as shown in the red boxes. Once you click the paper clip icon, the RTA checklist addendum PDF will be displayed as shown by the red arrow. You do not need to provide a response to the observations in your RTA response in order for your submission to be accepted. However, addressing these questions could help facilitate the substantive review of your submission.

Before you submit your 510(k) submission, we highly recommend that you proofread your final submission. This will ensure consistency throughout. Also, please ensure the primary contact information is correct and identify an alternate contact. If clarification is ever needed regarding your not-accepted submission or your 510(k) submission in general, please feel free to contact the lead reviewer. Also, if you do not receive an RTA decision

within 16 calendar days of your original submission, please e-mail 510(k) staff for a status check of your 510(k) application. The 510(k) staff e-mail is 510(k)_program@fda.hhs.gov.

In conclusion, if you try to incorporate these best practices in your submission, there is a greater chance that your submission will be accepted during its initial review. This concludes my presentation. Thank you for listening, and we are available to take questions you may have.

MS. STAROWICZ: Great. Thank you so much, Brittany, for walking us through this very important topic and really helping us to understand how companies can successfully navigate the waters of the RTA process and reduce the likelihood of receiving an RTA hold.

And I think this is a really nice lead-in to our first industry panel discussion on eCopy and RTA, and this will be one of three sessions that we'll have today, probably a little bit less structured than some of the more formal presentations that you've seen. But I'd like to just first of all introduce my esteemed, distinguished panelists that I have here today with me, and we'll start with Alexia Haralambous.

Alexia obtained her bachelor's and her master's degree in biomedical engineering from Johns Hopkins University, and she spent three and a half years at FDA as a premarket reviewer of spinal devices focusing primarily on anterior spine and intracolumnar devices. She joined the regulatory affairs team at Stryker's spine division about three years ago, and she's currently a senior staff regulatory affairs specialist providing global regulatory strategies for new product development, supporting global compliance initiatives, and aiding and sustaining production and marketing efforts.

My next panelist is Allison Komiyama. Allison obtained her bachelor's in molecular biology from UC Berkeley and her Ph.D. in neuroscience from Stanford University. She has worked in regulatory affairs since her time at FDA from 2010 to 2011, and in 2014 she started her own business, AcKnowledge Regulatory Strategies. It's a consulting firm that

focuses on U.S. submissions for medical device manufacturers. She earned her RAC in 2014, and she's the founder of the Regulatory Alliance Forum, which is an annual conference that brings together medical device manufacturers and regulatory professionals.

And last, but certainly not least, we have Caroline Rhim. Caroline obtained her degrees in materials science/engineering and biomedical engineering from MIT and Duke University. She is currently executive director with NSF International where she provides regulatory strategy and submission support to medical device companies. Prior to NSF, Caroline spent over seven years in the premarket review divisions at CDRH, and most recently as part of the spine division.

So, I'd like to welcome again Alexia, Allison, and Caroline to the panel.

So, we're going to focus most of our time here within the next 25, 30 minutes or so on RTA, the RTA process. And this is an area, as you know, of particular importance to medical device companies as we're all striving to compile good quality submissions and seek that predictable and timely FDA decision on our submissions.

So it's hard to believe the RTA process was actually initiated almost, I guess, about eight years ago at this point, with a specific goal of promoting complete submissions, you know, really maximizing the efficient use of time both on the reviewer resources and industry resources, reviewing -- I should say reducing the number of review cycles, and then ultimately to get to a decision on that submission in a timely manner. And this was especially important at the time for FDA to meet specific performance goals that had been established through the medical device user fee legislation. Since that time, we've seen, in general, the rate of RTA rejections declining, but there do remain, however, some areas of -- common areas of rejection, and FDA has outlined a few of those today.

So, I'd like to invite Allison, Caroline, and Alexia to jump in with some answers to questions. I did find out, interestingly of note, that they have not only unique experience as

former FDA reviewers now working on the industry side, but they've also worked at FDA during different periods of RTA implementation, so they bring that unique perspective to this discussion, as well.

So, to kick things off, then, my first question would really go out to Caroline. And so, Caroline, from an industry perspective, do you believe the RTA process has really met its intended goal of enhancing the overall efficiency and timeline for FDA review, and if so, can you give us a few examples?

DR. RHIM: I think, as Sharon mentioned, the RTA process has certainly seen evolution over time, and having observed this process over the years and with many of the initial inconsistencies that have been worked out, I would say that its goal to enhance the efficiency and timeline for FDA review has been met.

I think if we look at where and how the Agency has dedicated a lot of its resources, it's really towards making that entire review process and overall timeline as streamlined as possible. So, with the RTA program, the big push was towards letting industry know what FDA's expectations were. So, you know, from the industry perspective, we were really forced to address each of these review elements in a submission, importantly ensuring consistency, which was actually a problem with many submissions coming in the door to FDA. And these help tackle some review issues before even coming in with your submission.

So, these baseline expectations, even from, you know, having -- some of the examples that I can think of are having to address shelf life or sterilization or processing for accessories, for example. Knowing that, that information was necessary really helps guide industry to include the appropriate information, at least as a start. And then, with the added addendum, it's also been helpful to some degree to know what substantive information is needed to move forward.

MS. STAROWICZ: Great, excellent. Thank you, Caroline.

Actually, the next question I'll ask I will pose to all of you: What specific areas of the RTA process do you believe continue to remain the most challenging for manufacturers?

Maybe, Alexia, I could ask you to go first.

MS. HARALAMBOUS: Yeah, sure. I would say that getting substantive questions during the RTA process can still be a bit of a challenge for manufacturers, so getting the early awareness about the information that's missing can certainly be helpful, but the time it might take to respond to some of the substantive questions during RTA could throw off the company's planning and project timelines.

I think, also, there can be certain elements of a 510(k) in which it's not immediately clear which details could qualify as an administrative first substantive component, so like even after reading some recommended elements in the special controls guidance document. So kind of one example that comes to mind is, in the interbody guidance, there is a recommendation that we provide our test reports -- within our test reports like a description of the testing configuration and the testing environment, and it really hasn't been too much of an issue for us, but I think that can definitely be a source of confusion for some manufacturers. Basically, the question of what would qualify a testing configuration description as administratively complete, like which specific elements of the configuration need to be explicitly called out in order for the description to be administratively complete.

So, I think it's important to note that maybe we may not perceive certain elements, for example, like an intradiscal height callout, as a key administrative element of a testing configuration description, but maybe the reviewer does. So that's kind of one example of like a potential source of confusion for manufacturers when we get a substantive question that may actually be perceived by the FDA reviewer as an administrative question. So that also kind of goes back to Caroline's comment, too, about just making sure we really

understand FDA's expectations.

MS. STAROWICZ: Right, great. All great points.

And, Allison, what are your thoughts on this question?

DR. KOMIYAMA: Sure. So, I think one of the -- I work with a lot of small startup companies, and I think one of the things that is a big challenge for them is when the milestones or the financial timelines for the company are really tied up around the submission time and also the acceptance of the file.

I think there's a lot of confusion around the word refusal. You don't hear -- if your company says, oh, our 510(k) got refused, what does that mean to investors, you know, what does that mean to upper management of the company?

You know, one of the benefits of the RTA is you get an administratively complete file that gets accepted. And I always say to companies, and I think this is based on FDA's metrics, is once the file is accepted, you have a 96%, I think, likelihood that you will get cleared, so that really helps them then gauge how much funding and then how much time they have until clearance.

I think one of the other challenges we've faced is if there are new reviewers who are working through an RTA response and we resubmit, you know, if there is a new reviewer or if there are still outstanding issues, you can get multiple RTAs. I was going through my old files, we had one that had four items that had been listed in an RTA letter. And then we responded, we received a new reviewer on the file because the previous one had left the Agency, and then we got nine new RTA-able elements in the second RTA. And I think that was very challenging for the company to figure out okay, how do we move forward? How much funding do we have to take care of these nine new deficiencies that they had to take care of? So, I don't bring that up to point out that I'm a terrible consultant, but more than -- it can be really hard to judge what sort of time we're looking at with RTA.

MS. STAROWICZ: Everybody's figuring it out together.

So, shifting gears a little bit, let's talk about the difference between specials and traditionals relative to the RTA process. They certainly all have their own unique set of challenges, but in your experience, what are some of the areas that are most often cited as reasons by FDA for an RTA hold, and do you feel those are always warranted?

Alexia?

MS. HARALAMBOUS: Yeah, sure. I can talk about specials. So, my group at Stryker does submit a lot of specials. Just due to the nature of our products, we have a lot of line extensions, expanded indications, et cetera. So, the special 510(k) program really has been wonderful in terms of allowing companies to expedite smaller changes or line extensions.

I would say, in my experience, I have noticed that probably one of the most commonly cited reasons for a special RTA hold is related to requests for more detail on verification and validation activities in design controls activity summary. So sometimes I would say the information requested during RTA hold can even border a little bit on the level of detail of a full test report. Sometimes there's a request for more info on test conditions or sample size, and that actually makes sense because sometimes you really do need that context to review certain changes. But in those cases, we do really feel the need to be cautious so as not to trip the conversion of our special into a traditional 510(k).

And more recently, too, I've learned that there are situations in which you can submit a full test report without having your special converted as long as the test report can be reviewed in a summary format. So, I think it's important for the reviewer to clarify some of the intention for the additional detail requests, like in the V&V information in a special, as well.

And then I would say, also, one other area that I've noticed, too, for special RTA holds is the request for redlines of proposed labeling, instructions for use, surgical

technique guides. So, the current special 510(k) checklist does require that the changes to labeling are highlighted or prominently identified. And there's also a line below that that's actually an additional recommendation that redline copies be provided. From my experience, that recommendation for redline labeling and surgical technique guides, that alone has been a reason for an RTA hold.

So, I agree with that recommendation, too, and in my opinion, I think it should really be more of a required element for the checklist because it's definitely warranted; it does make the reviewer's life a bit easier, as well. So that also has sort of become a standard component of our special 510(k)s.

MS. STAROWICZ: Great, great.

And, Allison, I think you do a lot of traditional 510(k)s and have experience with that. Do you have any additional comments to add?

DR. KOMIYAMA: Sure. For traditional 510(k)s, definitely pay attention to device-specific guidance documents that are out there, and make sure you follow what guidance is in there. So, if there's specific labeling or testing that is necessary for that device, don't forget to include it.

Also, I know that there's been a lot of clinical testing that's been included in 510(k)s recently, so including the correct forms as well as the correct statement about general -- or I'm sorry, GCP and for animal testing. Also include in the statements about GLP testing.

I do think most of the RTA items are warranted. There are a few times where I felt confused by a question. You know, one of them was asking -- we had submitted an instructions for use as well as a surgical technique guide, and one of the RTA-able elements was that we had forgotten to include a user manual, and we wrote back -- you know, I talked to the lead reviewer and I said, we've already included the other two, and he said, oh, you're right; go ahead and ignore that piece. So, most of the time they're warranted

and they're very helpful to figure out how to move forward with a complete 510(k).

MS. STAROWICZ: Great, great. Thank you.

I want to talk a little bit about the intent of the RTA process being more of an administrative review process, you know, looking at the completeness of a submission versus getting more into what would be considered more substantive review, and sometimes the lines tend to be a little bit blurred there. We heard Brittany talk a little bit about RTA addendums and that FDA, in some cases, is issuing those as part of the RTA correspondence.

Caroline, I'd just love to know your thoughts. What are you hearing, at least from the industry side? Is this something that's being welcomed, or do you feel there's confusion?

DR. RHIM: Overall, I think it's welcomed. I think, you know, Allison will probably speak to where it's really kind of helped industry through. I think when -- I'm thinking of some cases. I think the, kind of the "please consider those observations" can also be confusing to sponsors even though it's clearly outlined as to what the purpose of those addendums are. But depending on how prescriptive the feedback is, you'll get some sponsors who preemptively, for example, jump on a request for testing when it might not have actually been required, but they've kind of taken this to be a complete kind of substantive review even though we say it's not, but they kind of jump the gun there.

We also get others who want to discuss each possible response with FDA prior to the SI review, prior to that being complete, or those who actually use this as an opportunity to be mini pre-sub in a way, to get additional feedback. So, you know, it would be interesting to hear FDA's feedback on their interactions with industry on that point. But I think, when we talk to different manufacturers, their responses to the addendum are generally, you know, it's an "it depends" situation because the type of observation will drive how best to

respond. So, it's always been clear that FDA wants to use opportunities to clarify any confusion, so if there is any, we always recommend reaching out to the reviewer for clarity before building your response strategy.

MS. STAROWICZ: Okay, great.

And, Allison, do you have anything to add to that?

DR. KOMIYAMA: Yeah, I think the addendum has been very helpful. I think it's not always clear where to find it, and I feel like the first one I ever received was -- we missed it completely, you know, the reviewer. After we had submitted the RTA response, the reviewer said, "By the way, did you see the addendum?" So ever since then, I make sure to check, but it's always helpful for FDA reviewers to let us know, if they are able to, that hey, there is an addendum included either in a second e-mail or in the RTA e-mail that goes out.

I think one of the benefits of understanding what might be coming down the pipeline during the substantive review can be very helpful. It also, I'm sure, helps them with shared time or the shared goals between FDA and industry because essentially, if there's a lot of the substantive information or review information is going to be needed, let's put it into this addendum, and you can continue working on it through substantive review process and have it ready to go if and when an AI letter or the hold letter comes. Essentially, you can turn around the response quite quickly and hopefully reduce the time that you're getting to market. And I know that also helps with, as I said, the shared goals between FDA and industry.

MS. STAROWICZ: Great, excellent.

Alexia, a question for you. Just curious to know what you've heard from the industry colleagues' perspective, particularly business partners such as other product development team members, their perception of the RTA process and, you know, how does industry actually use the process to establish its own key performance indicator metrics? Love to

hear what you're hearing.

MS. HARALAMBOUS: Sure. I would say at this point, most of our business counterparts, particularly like R&D, they're quite aware of the RTA process since, as you mentioned, Sharon, it has been eight years now since its inception. So, they're aware, at this point, that being placed on an RTA hold will introduce at least a few additional weeks into the overall expected timeline to clearance.

So, for example, like if we're preparing to submit a 510(k), let's say we've completed all primary guidance recommended testing, so if we take an interbody device again, as an example, we've done our ASTM F2077 testing, our F2267, et cetera, testing. But like, let's say we want to supplement it with some additional testing that's not always required but maybe could be helpful to the 510(k) review, and it's going to be conducted anyway, so I'm talking something like a characterization testing, maybe like a wear particle analysis. But let's say that testing is not yet completed; it will take maybe at least a few more weeks to months to complete. In that kind of a situation, there is quite a bit of deliberation about how much of our timeline we're willing to compromise.

We usually have a couple scenarios there. So, like one scenario could be okay, let's go ahead and submit the 510(k) without that additional testing up front. While running the risk of being put on an RTA hold, let's say we get an RTA hold, then we're going to have to wait for that additional testing to be completed before we respond. So that could set us back weeks to months. Another scenario could be, again, like we submit without the additional data up front, and let's say we actually make it through RTA, but maybe we'll get like an AI deficiency later on, but we'll at least have the additional testing completed by that point. So that would sort of be like a shorter scenario. And then another scenario would be well, why don't we just spend all the extra time up front, just get all that additional testing done and completed and then submit -- go ahead and submit that all together up front in

the 510(k). So I would say there is quite a bit of deliberation about whether or not providing a certain piece of information up front could increase the overall timeline due to getting an RTA hold.

And then I would say to the second part of your question, Sharon, regarding TPIs, the primary metric that we use to track STPIs are with regard to the overall 510(k) review process, including both the amount of time it takes for the 510(k) review itself, as well as the time required to respond to questions. So, we generally don't use the RTA timeline itself as a metric alone, we're more kind of the overall 510(k) review process.

MS. STAROWICZ: That makes sense. Great. Thank you, Alexia.

Well, I see we have about seven or eight minutes left in this session, and I wanted to give you all a few minutes in closing just to share any particular tips, pearls of wisdom that you have, to really achieve a successful RTA process for your submission.

So, Allison, would you like to go first?

DR. KOMIYAMA: Sure. Yeah, I'd like to echo something that Brittany said during her presentation, which was to include the RTA checklist when you submit your 510(k) and also fill it out, make sure that you're actually addressing each point as best you can, and then also include all the page numbers where things can be found. You know, as Brittany said, it might not be -- they're not going to tear it out and use it as the RTA checklist that they use. However, if there's anything that they can't find in particular, they might be able to reference the RTA that you fill out and see if there's somewhere in the document that oh, yes, there it is, and they can check that as complete.

I also feel like there is, you know, as I mentioned earlier with getting a new reviewer the second time around, I feel like reaching out to the review team or asking if there are any clarification questions on the RTA checklist that you get, you know, I always have felt that the reviewers are very interactive and willing to talk to you at that point and really help

you understand what's missing and how to fulfill the request. So, talk to them, and I feel like that would've definitely helped me with them, you know, knowing that there was a new reviewer or if there was anything we could've addressed ahead of time, that time in that file, so --

MS. STAROWICZ: Caroline, what about from your perspective?

DR. RHIM: I think, you know, one of things that I realize is how the balance of information that's included is actually really challenging, and I think with FDA, it seems like very straightforward to ask -- you know, to just provide a comprehensive device description. But now that I've seen some of the challenges with device development and how complicated that process can be, I can certainly see the struggle with how much information to include, and you always say how much of the story we need to convey.

So understanding that the product development cycle can take place over the span of years or through company acquisitions or supplier changes, through combining different device components over different projects, you know, you see tweaks in your user needs and design inputs, I guess sometimes the documentation is not as neat and as organized as you would like.

And while we often view a 510(k) as really a snapshot of this final finished device, there's a lot of history and documentation that has to be summarized and presented. So, there's something that's, you know, too much information or too much of a story that can make it even more confusing, and that's sometimes where you see a lot of inconsistency in the submission.

So, while some 510(k)s and their development process have been very nice and neat and straightforward, others haven't. And so, project teams really, even as interdisciplinary as they are, they really have worked on a project sometimes for so long that nothing is unclear to them. So, I always recommend to have somebody not familiar with your product

or kind of your area to read your file and have -- you have fun with the RTA process and have somebody kind of independent to look it over because there are areas that are confusing that somebody else might pick up on. So, in those cases, they'll pick up, and you'll be able to resolve those before coming in to FDA.

So you'll also get into situations, actually, where -- and Allison had touched on this, where you may not agree with your RTA or you may be confused about an element, but we always say we recommend, and I completely agree, that you reach out to the reviewer first, that it seems really intuitive, but there are definitely people out there who are really eager to get upper management involved. But in general, we advise against that because FDA has been very open to communication.

MS. STAROWICZ: Great, excellent. All important points.

Alexia, do you want to take us home and share any final thoughts?

DR. KOMIYAMA: Yeah, sure. So, I'll kind of echo what I mentioned earlier during this discussion about how "recommended" guidelines in the RTA checklist -- I'm specifically thinking of the special RTA checklist -- should really be treated as required elements. So, for specials, you should definitely be providing redline copies of your labeling and surgical technique.

I would say one other tip I would suggest is to definitely pay attention to your device-specific guidance and be sure to include those elements when compiling your submission and when you're evaluating your own submission for completeness prior to submitting to FDA. Even if those guidance documents are a little older -- I know spine has a couple guidance documents from the early 2000s, but those are still completely applicable, and I think it's important to include all of those elements in your submission.

MS. STAROWICZ: Great, excellent.

Well, many thanks to all of you. I think this -- we could probably go on for another

30 minutes, which we don't have on the agenda, but I think we -- you all were very successful in imparting your knowledge and experience to all the folks on the phone here today, giving us a lot of good pointers and tips. So many thanks, Alexia, Caroline, and Allison, for your participation in the panel. Thank you.

At this point we're going to move the program into a little bit of a different turn. I know there are many people out there, and I'd like to start by introducing Colin O'Neill, who will kick us off, and he's actually going to be leading us through an interesting audience participation survey on eCopy and RTA.

But first of all, Colin obtained his master's in biomedical engineering at Catholic University after completing his bachelor's degree in mechanical engineering at the University of Delaware. He's been at the FDA for about 12 years and is currently Acting Assistant Director in the Division of Spine Devices within the Office of Orthopedic Devices.

So, Colin, we're anxious to kick this off with you and find out more about the survey tool.

MR. O'NEILL: Thank you, Sharon.

So, we're going to do these Mentimeter questions, and I want everybody to know that there is a delay between the live production and webcast, so we're going to ask each question and wait a bit to allow people to answer. Feel free to send follow-up comments and questions to our mailbox at OHT6-Feedback@fda.hhs.gov. Answers to all these questions and follow-up comments will be very helpful for our respective program areas and efforts.

So, we'll start with the first question. The first couple questions are yes or no, easier answers, and then we'll get into some freeform response questions. The first question is: Are the technical standards required of an eCopy that are outlined in Attachment 1 of eCopy guidance clear and understandable?

So again, we're going to wait for the delay to occur and answers to come in and then we'll move on to the next question.

Great, I see a lot of answers coming in. Overwhelmingly yes. They are clear and understandable, and that's great. So yeah, given those answers, I think we can move to the next question.

So, the next question is: Do you use the current eSubmitter tool to create your eCopy?

Okay, looks like mostly no, but a number of yeses. And please feel free to use this down time in between questions to send any questions or feedback you have to the e-mail box. Again, that's OHT6-Feedback@fda.hhs.gov.

Okay, great. Answers seem to be stabilizing. All right, let's move on to the next question: Do you use the eCopy validation module on the FDA's website to test your eCopy prior to submission of your eCopy?

I'm not seeing too many responses. Maybe we'll take that as a no. I believe it's not any technical difficulties. Okay, let's move on to the next question. So, this is a freeform response question: Please provide a one-word response regarding your thoughts about eSTAR.

Overdue, fabulous, helpful, good idea. I agree, it's very exciting. Would be very helpful on both sides. Concerned. If you would like to elaborate on any of your comments, please e-mail the feedback mailbox.

This is really great. Okay, let's move on to the next question. This is another freeform response: What types of RTA deficiencies have you received during the substantive review that you believe should be flagged at the RTA review phase? This is following up a little bit from the discussion prior.

So again, these types of items could be in the addendum of the RTA, just

observations that the lead reviewer has made and wanted to communicate early on in the review phase.

Great, lots of good comments. Okay, let's move on to the next question: So, do you believe FDA RTA reviews are consistent across all the divisions within OHT6?

Okay, I'm starting to see somewhat of an even distribution, lots of responses still coming in. This is very helpful to us. For items that are inconsistent, we really appreciate feedback be sent to the mailbox for us to address. Thank you.

Seems like responses are stabilizing. Looking forward to any additional feedback anybody else has. We'll go on to the next question. So, this is another freeform response: Do you have any briefly-stated feedback for OHT6 with respect to eCopy, eSTAR, or RTA elements in 510(k) submissions?

Great, lots of great helpful comments. We're hoping to roll out eSTAR as soon as we can. We have a little bit more time in the session, so I'll leave it open for people to provide more comments to this question.

Keeping eSTAR simple rather than complex, great suggestion. Again, hopefully eSTAR eliminates some of the administrative busy work on both ends for industry and reviewers, so hopefully that will minimize time to clearance, as well.

Great. Well, I think comments have slowed down a bit. I'll throw it back to the studio to go to the next section. Thank you.

MS. STAROWICZ: Great. Thank you, Colin. And many thanks to the audience for your participation, as well. There will be several other opportunities throughout the day today to have you weigh in on other topics, and I just really would encourage everybody to please participate because this will capture valuable data for both the FDA as well as industry.

So, we'll now switch gears a bit and hear from our next FDA presenter,

Charles Warner, and Charles will cover device descriptions and indications for use, a very important and meaty topic. Charles Warner obtained his Master of Science in biomedical engineering from the University of Michigan in 2014. He has served at the FDA for six years as a lead reviewer in the Extracolumnar Spinal Devices Team of the Division of Spinal Devices within OHT6.

And so, Charles, the floor is yours.

MR. WARNER: Hello, my name is Charles Warner, and I am a lead reviewer in the Extracolumnar Spinal Devices Team of the Division of Spinal Devices within OHT6: Office of Orthopedic Devices. My discussion is titled "Device Descriptions and Indications for Use Statement: Clear Yet Concise is Best." Our goal is to highlight how to effectively and efficiently document descriptive information in a 510(k) premarket notification submission for a spinal device.

I will start off by discussing requirements to consider outlined in FDA guidance documents, 510(k) forms, and device regulations. Then I will detail what descriptive information to provide per these requirements for a 510(k) spinal device and end with some best practices to consider. Afterwards, I will follow the same discussion pattern for the indications for use statement.

If you're wondering where to start looking when drafting a 510(k) submission for a spinal device, the requirements listed here are best. I have included links for this information on this page for your reference.

As discussed in an earlier presentation, the RTA checklist elements need to be addressed in order for FDA to continue with substantive review of a 510(k) submission. To help understanding, I will expand upon the requirements outlined in the RTA checklist in relation to device description and indications for use statement.

RTA element numbers are taken from the RTA checklist for the traditional 510(k),

although the requirements are the same as for a special 510(k). Importantly, the RTA checklist refers to any applicable FDA guidance document for which I will go through the three listed here: the 510(k) Program Guidance, Spinal System 510(k)s Guidance, and Class II special controls document for intervertebral body fusion devices.

Furthermore, the device regulation is also important to consider when describing a device and drafting the indications for use statement. The five main regulations we currently have for various spinal devices are listed here.

Now let's delve into device description. A good place to start is the general FDA guidance on the 510(k) program, which provides a general overview of key descriptive information to include. Mainly, the overall description of the device should include engineering drawings or illustrations, and this should include diagrams for interconnecting components, details of physical specifications such as dimensions and tolerances. Additionally, outline design and function of significant device features should be provided.

Furthermore, complete information of the device materials should be provided, including chemical formulation, additives, surface coatings or surface modifications, and material processing such as the type of manufacturing. Examples of the type of manufacturing may include subtractive or additive manufacturing. For devices utilizing energy sources or software or hardware, these features should also be described. Additionally, other unique features such as porosity and degradation characteristics should be specified as applicable for your device.

This brings us to specific device description requirements in the RTA checklist. RTA Element 12 refers to device-specific guidance, special controls, or device-specific classification regulation information.

Review of the scope of the spinal system 510(k)s guidance reveals -- is considered a device specific guidance for plate- and rod-based spinal systems for fusion such as pedicle

screw systems, anterior plating systems, and for vertebral body replacements. Notable spinal devices excluded are facet screws, interbody fusion devices or spinal cages, and spinal devices intended for non-fusion. With that being said, the general device description elements would be helpful to provide for any spinal device.

Starting off, the purpose of the 510(k) should clearly be stated. For example, you should state whether the 510(k) seeks clearance for a new spinal system, adds or modifies components to a cleared spinal system, or proposes other modifications. For purposes other than introducing a new spinal system, we recommend the purpose identify and briefly describe all changes since the previous clearance, including any add-to-file changes. For specific device description information to provide, all device or system components should be listed in a table of components. For each component, engineering drawings and a written description should be provided. Relevant descriptive information includes device sizes, dimensions, geometry, and interconnection with other components or subcomponents.

In particular, the mechanism and purpose of interconnecting components should be described and supported with the relevant illustrations. Helpful illustrations may include cross-section images, exploded-view drawings, or 3-D PDFs. Specific to anteriorly- or anterolaterally-placed spinal devices, the profile of the device should be compared to a predicate device to support substantial equivalence. To help understand intended use of the device, illustrations of the device on a spinal model and various representative surgical uses are recommended.

Continuing on, device materials should be identified, including any voluntary material standards to which the material conforms to. Identification of the material standard also helps to understand manufacturing considerations for the device. For example, ASTM F136 for raw titanium alloy or ASTM F3001 for additively manufactured

titanium alloy.

In relation to accessories, instruments specific or unique to the device should be described similar to the recommendations as just discussed for implants, including the instrument list, illustrations, and materials information.

A table of components helps facilitate listing components in a 510(k) submission. We understand some spinal systems, such as pedicle screw systems, consist of many components with a multitude of varying dimensions. Even so, all components of the system should be listed, including those components that have received prior 510(k) clearance. We recommend a column identifying the 510(k) number for previous clearance or distinguishing components as new. Highlighting or different shading is also helpful to differentiate between new and previously cleared components. Sample formatting of a table of components from the spinal system 510(k)s guidance is copied here. Furthermore, it is important to note that the table of components represents all components seeking 510(k) clearance. If, for any reason, device components are withdrawn from a 510(k) submission, an updated table of components will be requested.

Moving on to special control requirements, intervertebral body fusion devices have their own special controls guidance document. Much of the device description requirements are the same as recommended in the spinal system 510(k)s guidance, such as providing a written description; identifying device sizes, dimensions, and geometries; including engineering drawings and relevant illustrations of the device and images of the device on a spinal model. Again, material specifications and the conforming standard are also to be described.

For instruments specific or unique to the implantation of the device, similar descriptive information should be provided such as name, functional description, illustrations, and materials information. Of note, for instruments that are exempt from

510(k) requirements, we recommend that you indicate its classification regulation and provide reasoning for the Class I designation. An example regulation for Class I orthopedic manual surgical instruments is listed here.

As many interbody devices are manufactured from various polymers, it is important to characterize the material composition of the interbody device, including the material source and purity. Supporting information may include a certificate of analysis, material safety data sheet, or authorization letter to reference a device master file. A master file is a way for the material provider to preserve trade secrets while facilitating sound, scientific evaluation of the material to support numerous marketing applications from various companies.

Information in a master file for a material may include specifications, characterization, and testing data, among other information the master file holder or FDA deems important to the review. The letter of authorization from the master file holder to a client should utilize a company letterhead and stationery, and specify the master file number, page numbers or content sections applicable or restricted for review. The client name and the device name of the client should also be provided. A link to information on master files is on this page.

Material characterization of the polymer should be on the final sterilized material. Relevant descriptive information should include leachables, material properties, molecular weight, molecular weight distribution, chemical and crystal structures, percent of crystallinity, and degree of cross-linking.

In summary, for interbody devices, please remember it is important to describe device and material characteristics.

For a 510(k) device, the classification regulation may identify special controls to abide by. For instance, both 21 C.F.R. 888.3070 and 21 C.F.R. 888.3075 for

thoracolumbosacral and cervical pedicle screw systems have special controls that the design characteristics of the device, including engineering schematics, must ensure that the geometry and material composition are consistent with the intended use.

One aspect of this meaning entails ensuring that the surgical technique of the device is consistent with the intended use and does not describe any implantation techniques that go beyond the intended use of the device. Examples include review of the device dimensions and spinal levels of fixation or material composition and fusion versus non-fusion techniques.

These past eight slides were all discussing device description requirements for one RTA checklist element for various spinal devices. It should be noted that those requirements overlap with requirements specified in further RTA checklist elements. In short, if you address recommendations in the spinal system 510(k) guidance or special controls in the form of guidance or classification regulation, then you are likely to address the requirements in other RTA checklist elements.

For RTA checklist Element 13, this is ensuring that the device description is consistent throughout the submission, including relevant labeling documents.

Continuing to RTA checklist Element 14, these requirements are repetitive, so you should provide a functional description of the device to achieve its intended effect and description of surgical technique, including anatomical location and interconnecting components. Information to provide also includes a list of components and representative engineering drawings and illustrations.

It is important to note that for devices that are compatible with other previously cleared devices, all compatible components should be described along with the interaction between the subject components and other devices. This information is important in understanding the mechanism of action for the intended use.

RTA checklist Element 15 is the last element for device description and pertains to device accessories such as instruments. As previously discussed, a list and description of all accessories should be provided along with identifying whether or not the accessory has received prior clearance.

In conclusion for device description information, I want to highlight some elements to help ensure information is clear, yet concise. Starting off, the purpose of the submission should be stated and clearly summarize all changes. Device and component description should both be written and illustrative, especially for key technological features. For example, cross-section images are helpful to understand interconnection mechanisms and lattice structures. Exploded-view drawings are also helpful for describing expanding features. Device specifications should be indentified such as sizes, dimensions, and relevant geometry. The table of components should list all components and be consistent with the device description. Furthermore, information should be consistent with labeling documents and ensure the surgical technique is within the intended use of the device. Unique device processing should be identified such as additive manufacturing. Lastly, as will be discussed more in-depth later, all add-to-file changes since previous clearance should be identified and described.

Let's move on to the indications for use statement. First, it is important to distinguish the difference between the meaning of intended use versus indications for use. Per the 510(k) program guidance, for purposes of substantial equivalence, the intended use is defined as a general purpose of the device or its function and encompasses the indications for use. Meanwhile, the indications for use is defined in 21 C.F.R. 814.20 as the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended. For examples of the difference between intended use and indications for use, please refer to the 510(k) program

guidance document.

Starting with RTA checklist Element 3, you should include an indications for use statement and designate for prescription use or over-the-counter use. Note that orthopedic implants are prescription use devices. The recommended format for the indications for use statement is Form FDA 3881, as shown here. We recommend to print and PDF this document to remove the blue background and include in the submission in this format.

Next, RTA checklist Element 18, part (a), specifies for the indications for use statement to be identical throughout the submission. It is important to note that for purposes of review for substantial equivalence, the wording of identical versus similar have different meanings. For example, similar implies there are differences, whereas identical does not. In the case of consistent indications for use, it should be identical throughout the submission.

When looking at the spinal system 510(k) device-specific guidance, we recommend that you explicitly state the indications for use statement at the beginning of your submission. Also, we suggest that you avoid open-ended indications. For example, please avoid listing the following generic indications: instability, disc herniation, or general spinal curvature.

Also, the spinal system 510(k) guidance lists indications for use for devices within the scope of the guidance, such as pedicle screw systems, anterior plating systems, and vertebral body replacement devices. Various device-specific classification regulations might also include indications for use covered by the regulation. In relation to spinal devices, both 21 C.F.R. 888.3070 and 21 C.F.R. 888.3075 for thoracolumbosacral and cervical pedicle screw systems, these list indications for use. Please refer to those regulations for the complete list of indications.

In conclusion, I again want to highlight some elements to help ensure the indications for use statement is clear, yet concise. First, please ensure consistency throughout the submission. If not consistent, it is difficult for an FDA reviewer to know which indications for use statement is being proposed. For conciseness, we recommend avoiding extraneous information or open-ended indications. For example, the indications for use statement does not need to include information that is contained within labeling elements, such as descriptive information or surgical technique considerations.

MS. STAROWICZ: Great, thank you. Thank you very much, Charles. You certainly covered a lot of great information. You've shown us how clear yet concise is best, and I would also add consistent to the list, as well.

So, at this point in time, we're going to move to take a short 15-minute break. We just ask everybody to please be back by 9:50, and we'll jump back into our program. Thank you.

(Off the record at 9:34 a.m.)

(On the record at 9:49 a.m.)

MS. STAROWICZ: Welcome back, everybody. I hope you all had a little bit of time, at least, to stretch your legs and maybe refill your coffee cup.

I'd like to now introduce our next presenter as we continue our program here this morning. Our next presenter is Aakash Jain, and his presentation will cover how to go about addressing changes to an existing device, so I'm sure everyone will want to pay very close attention to this. Aakash obtained his master's degree in biomedical engineering from Stevens Institute of Technology, and he's been at the FDA for over two years and is a lead reviewer in the Intracolumnar Team. Prior to joining FDA, Aakash worked in the medical device industry as a regulatory affairs professional for over eight years.

Aakash, you have our undivided attention.

MR. JAIN: I'm Aakash Jain, and I serve as a lead reviewer within the Intracolumnar Spinal Devices Team of the Division of Spinal Devices within OHT6: Office of Orthopedic Devices.

My discussion is titled "Changes to an Existing Device." I will start off by saying that this topic does not supersede and/or provide new information that has not been previously published. This presentation is based on the FDA guidance document "Deciding When to Submit a 510(k) for a Change to an Existing Device." We will discuss examples of when a 510(k) is and is not required followed by reporting the changes. If you are wondering where to find information if your device modification requires a 510(k) or not, please read the FDA guidance document as well as the presentation that is posted on CDRH Learn. I have included links for this information on this page.

Section IV of the FDA guidance document includes guiding principles. I won't read the entire guiding principles but will emphasize the FDA requires a new 510(k) submission when the modifications could significantly affect the safety or effectiveness of the device, or the change is major, or modifications in the intended use of the device. The main types of changes are labeling, technology, engineering or performance, and materials.

When making changes, you would need to evaluate the risk profile to determine if the change needs a new 510(k). The evaluation of the risk profile should consider both safety and effectiveness since the regulation requires submission of a new 510(k) when a change could significantly affect safety or effectiveness.

Section E of the guidance document explains the risk-based assessment. We will not specifically go into details over the risk-based assessment as we understand that every manufacturer and every device has a different risk level and potentially different effectiveness level. We really wanted manufacturers to have the flexibility to use this guidance along with their own processes for their risk-benefit assessment for their specific

devices.

For a 510(k) determination, you would need to consider the impact of device modification changes on device labeling, technology, engineering, performance, and/or materials. When documenting your change, please assess each change as well as the cumulative assessment of all changes to the previously cleared device. For example, if you made a dimensional change post-510(k) to the lateral windows of a cage, and then a couple of months later, a dimensional change is made to the surface of the cage, we expect that you also assess both changes together and compare it to the previously cleared cage.

Just a side note here, if you determine that the device changes do not require submission of a new 510(k), you should document the decision-making process and the basis for that conclusion. We want to note that only highlighting the flowchart in the guidance document or simply answering yes or no to each question without further details or justification is not sufficient documentation.

We know that routine verification and validation is conducted and sometimes testing would be needed. If testing has been done, it does not necessarily mean a new 510(k) is needed. Occasionally, routine verification and validation activities may either produce unexpected results or otherwise prove to be inadequate to verify and/or validate the modified design. In such instances, a new 510(k) is likely required.

Please note that 21 C.F.R. 807.81(a)(3) requires submission of a new 510(k) for a change that could significantly affect safety or effectiveness. If the results of a risk-based assessment is that a change or changes could significantly affect safety or effectiveness, submission of a new 510(k) is required even if routine verification and validation activities are conducted successfully without any unexpected results.

Please also be aware that verification and validation requirements apply for all devices subject to 21 C.F.R. 820.30 and must be conducted regardless of whether

submission of a new 510(k) is required.

Here are some examples in which a device modification would not require a 510(k): introducing an intermediate size of the same design, for example, if you originally cleared a 6 mm and 8 mm diameter with the length of 35 mm thoracolumbar pedicle screw and wish to introduce a 7 mm diameter with a length of 35 mm thoracolumbar screw with the same design, that screw would not require a 510(k); tightening the tolerances on engineering drawings; and administrative labeling changes, such as formatting, correcting grammatical mistakes, would generally not require a 510(k).

Changes that do require a 510(k) is changes in material, such as going from PEEK to titanium alloy; switching from a subtractive to an additive manufacturing process; changing sterilization methods, such as going from moist heat steam sterilization to gamma sterilization. We recommend that you review Appendix A of the guidance document, which gives over 30 hypothetical examples that are intended to illustrate the process of determining when a 510(k) is required.

This brings us to reporting the modifications. When a new 510(k) is submitted for a device with multiple changes, that 510(k) should describe all changes that trigger the requirement for a submission. The 510(k) should also describe other changes since the most recently cleared 510(k), i.e. those that did not require submission of a new 510(k) that would have been documented as part of the first 510(k) for that device.

Just a note here. Even if a device modification does not introduce a new worst case or performance testing demonstrates equivalent performance, a 510(k) is still required if the new design goes beyond the dimensions design of the unmodified predicate device.

We wanted to briefly discuss bundling device modifications in 510(k) submissions. Bundling refers to the inclusion of multiple devices or multiple indications for use for a device in a single premarket submission. Devices can be bundled if the supporting data is

similar, involves one review division, and the indications for use is similar. We have accepted submissions in which multiple devices or indications for use were bundled when the device or indications presented issues that could be addressed during one review. However, sometimes it may not be appropriate to submit bundled submissions, and the Agency can unbundle the submission if we disagree with your bundled submission based on the guidance document.

So let's take a look at some examples. It would be acceptable to bundle a submission in which you are changing sterilization method, for example, going from moist heat steam sterilization to gamma for a multiple product area, such as cages and pedicle screw systems. It would not be acceptable to bundle a submission in which you are seeking clearance for two different product areas, such as a lumbar cage and a lumbar vertebral body replacement device. Essentially, you should consider the complexity of device design, technological characteristics, and the modifications being made to the existing devices for whether or not to bundle.

This concludes my presentation. Thank you for listening.

MS. STAROWICZ: Thank you so much, Aakash, for sharing FDA's perspective on how to handle device modifications that occur following FDA clearance, and also to share some insight on when it makes sense for manufacturers to consider bundling those submissions. So thank you.

You know, as regulatory professionals, we all strive to write the perfect submission, and our next speaker, Vikansha Dwivedi, will take us through the elements of what is considered to be a quality 510(k) submission. Vikansha has been with FDA for about four years, and before joining the Agency, she obtained her Bachelor of Science in mechanical engineering from the University of Maryland. She is currently a reviewer in the Intracolumnar Spinal Devices Team.

Vikansha, the podium is all yours.

MS. DWIVEDI: Good morning. My name is Vikansha, and I'm a lead reviewer in the Intracolumnar Devices Team. Today I'll be discussing the elements of a quality 510(k) submission. I will be focusing this discussion on a traditional 510(k) submission.

In my presentation, I will discuss submission elements and decision elements of a 510(k) submission, common deficiencies that can be eliminated through proper documentation and presentation of information, information organization, and lastly, how to present your AINN responses in situations where interactive review is beneficial to avoid decision lag or unfavorable decisions.

A 510(k) application is a premarket notification, and it is referred to as a 510(k), and the reason being is that it refers to the Section 510(k) of the Federal Food, Drug, and Cosmetic Act. Code of Federal Regulations 21 807 subpart (e) outlines information that is required in the submission of your application. It is a marketing clearance submission, and therefore the FDA clears 510(k)s, and this is based on the determination of substantial equivalence.

Your device compared to predicate device has the same intended use and technological characteristics. When there are differences in technological characteristics, which is generally the case, for example, device design, material, sizes, et cetera, are almost never identical to a cited predicate. These differences in technological characteristics do not raise different questions regarding safety and effectiveness, so substantial equivalence is the most important point of a 510(k) submission, and that's what you're trying to demonstrate through the information provided in your submission.

A predicate device is legally marketed, previously cleared by FDA, used to compare to a new device for the purposes of determining substantial equivalence per 21 C.F.R. 807.92(a)(3). The 510(k) guidance for industry and Food and Drug Administration staff,

issued on July 28, 2014, provides in-depth information regarding substantial equivalence evaluation.

Appendix A of this guidance provides a 510(k) decision making flowchart, which I have copied on this slide. And I don't expect you to be able to read this flowchart, but I wanted to discuss a few things regarding this flowchart in the following slides of this presentation.

A 510(k) submission has various sections, and in my presentation, some of these sections will be covered. This slide gives an overview of sections that will be covered in-depth during other previous or upcoming presentations in today's workshop. This slide gives an overview of sections that will be covered during this presentation. This opening section should be able to provide a clear and succinct overview description of your device. The purpose of the submission should be clear and not be left to be figured out by the reviewer. For example, be clear about the device, whether it is a new device or the submission is proposing changes to an existing device. If a system is brand new, state that it is a new system with new designs.

If the device is not new, provide a clear overview of all the changes being proposed in the submission. Include clear images of all device components and blow up images of proposed design changes. If there are labeling changes as part of the submission, be sure to include redline changes to labeling.

A 510(k) summary or statement should be provided with your submission. However, please refrain from providing both. Only one is needed since having both the statement and summary will necessitate extra back-and-forth at the time of clearance. Only one can be put on the public database after the clearance of your device. Make this choice at the time of your submission.

A 510(k) summary shall be in sufficient detail to provide an understanding of your

device. The summary should be in a separate section of the submission beginning on a new page and ending on a page that is not shared with any other section of the premarket notification submission and should be clearly identified as a 510(k) summary. Please make sure that the information provided in the summary is accurate, specifically submitter's name, address, telephone number, a contact person. Please always review to check the date the summary was prepared. They should be current.

Additionally, the name of the device, including the trade or proprietary name, common or usual name, and the classification name should be adequately provided. When listing predicates, please be sure to identify one and only one primary predicate, and other predicates should be listed as additional predicate or reference devices as applicable. Please do not include confidential notation on your 510(k) summary as this is a public document upon the clearance of your device. Providing it without the confidential notation saves time and back-and-forth towards the end of the review cycle.

The 510(k) decisions are based on substantial equivalence, and the conclusion part of the summary reflects that. Therefore, please refrain from deviating from the recommended verbiage. Too much information is not advantageous and might lead to unnecessary minor deficiencies and back-and-forth; therefore, it is best to stick to the prescribed information. The substantial equivalence table I showed earlier on Slide 5 is a tool to help you and reviewers make substantially equivalent decisions regarding your device.

Applicants often include this flowchart in their submission and provide a blanket "yes" to the various decisions identified in the flowchart. It will be more meaningful and helpful to provide discussions regarding the various decision points from the flowchart.

We understand that your device is not a mirror image of the predicates on the market and there will be differences between the two. It is important that you identify all

the differences between your new device and the predicate. For each identified difference, you should explain why the differences do not affect the overall substantial equivalence of the subject device as compared to a predicate device.

Additionally, performance data might be useful in demonstrating substantial equivalence with respect to specific differences. For example, if the range of sizes of the subject device is outside the range of sizes of the cited predicate devices, then you should provide the justification -- for example, anatomical, physiological -- to support inclusion of those components. This slide summarizes the recommended information that should be provided in your submission and will help the reviewers make substantially equivalent decisions regarding your new device.

This is an example of a table comparing the properties of a subject device with identified predicates. These predicates should be FDA cleared and consistent through the submission. Along with the tabular comparison, be sure to include adequate rationales and/or discussions for the differences. If you have cited and relied upon literature for your rationale, please be specific about the part of the article and how it addresses the differences.

This section provides user manuals, promotional materials, device labels, and shipping/packaging labels. Please provide labels for device and device-specific instruments. Sometimes the draft label provided for the devices may not apply to the instruments, specifically if the devices are provided sterile and the instruments are provided non-sterile to be end-user sterilized. Be sure to include both the sterile and the non-sterile labels respectively.

The surgical technique manual should provide details and magnified sketches of important steps. Please remember to provide the removal, revision procedures with specific details as they pertain to your device.

Indications should be a carbon copy of the indications provided in the 510(k) summary and indications for use statement. The package insert should include the stock MR language for devices that have not been tested or evaluated. This is very important and needs to be communicated to the user as it can lead to unintentional patient harm.

Please refrain from including claims like performance claims whether describing real or potential benefits. The Agency does not consider claims as part of a substantial equivalence determination.

Name and organize your files in a way that indicates their contents. Have a distinctive name that gives an indication of the content. Follow a consistent pattern. Avoid repetition of elements and information. Consistency is key. Organize files in a way that makes sense within the context of your device but would also make sense to someone who was not intimately familiar with your submission.

Please do not provide embedded files. This is often seen with test reports. What I mean here is that sometimes Appendix A has the test reports for mechanical tests, and embedded there will be reports of biocompatibility or MR testing. Please provide test reports for separate tests in separate sections and name them accordingly. Remember, a well-organized file will help us get to the information readily and avoid misunderstanding of your device.

Readability isn't about dumbing down your content. Of course, the content you are presenting is highly technical and complicated in nature, but making it readable will make it clear and easy to understand.

Regarding response to an AINN request, it is best to follow a question and answer format for the identified deficiencies. This should include all parts and subparts of a particular deficiency. For example, if Deficiency 1 has two parts, A and B, it is best that you address them in the same order. I have an example on the slide. Please be mindful that

these are fictitious examples and are only communicating the organizational aspect of your AINN response.

Here is an example of a response that follows the same order as the deficiency. The supporting information can be provided in appendices. These appendices should be cited in the response so that the information is easy to locate by the reviewer. In this example, the sponsor's response makes it clear that the change has been made and the supporting information can be found in such and such appendices.

There might be situations where you would like more clarity on the deficiency or you would like to discuss an alternate approach to address the deficiency. In such cases, please be proactive and try to start a dialog with the reviewer as soon as possible. Instead of submitting your supplement and then having disagreements about the approach, this will provide an opportunity for you and the reviewer to understand each other and have a plan forward. Explicitly addressing all outstanding issues is vital in your response as the AINN response could be deemed incomplete without this information. This makes it even more important to be upfront and proactive regarding your response. We are here to help and work alongside you; however, you know your device the best and can provide us with the necessary information to address the outstanding issues.

With that, I would like to end my presentation by saying that we are only an e-mail or a phone call away. We are always here to help and promote public health. Thank you.

MS. STAROWICZ: Thank you so much, Vikansha, for reinforcing these very critical elements of a quality 510(k) submission.

So we've heard a lot today so far about the importance of device descriptions and indications for use in a 510(k) submission and how they can impact a successful premarket review, and this will be an excellent segue to our next industry panel session. And today I'm honored to be joined by three distinguished panelists who each bring significant experience

and expertise to the topic that we'll be discussing today. So we'll start off with some introductions.

First of all, we're joined by Dr. Kelly Baker, who earned her Ph.D. in biomedical engineering and her master's degree in mechanical engineering from the University of Iowa, and has been involved in spine and orthopedic research, development, regulatory and clinical functions for the past 30 years. Dr. Baker has been with Globus Medical for 17 years, leading the company's regulatory and clinical efforts with more than 130 FDA 510(k) clearances, and she's the senior vice president of regulatory and clinical affairs. Welcome, Kelly.

Our next panelist is Glenn Stiegman. Glenn has a degree in biomedical engineering from Tulane University and a master's degree in bioengineering from Clemson University. Glenn has spent six and a half years at FDA as a lead reviewer and, eventually, branch chief in Orthopedics. He left FDA in 2006 to start MCRA with an initial regulatory focus in musculoskeletal therapies. He has since built a regulatory department that's focused on musculoskeletal, neurological, cardiovascular, and wound therapies, among others, and he's currently the senior vice president of regulatory and clinical affairs.

And our third distinguished panelist is Janice Hogan. Janice is a biomedical engineer by training, as well as an attorney specializing in FDA regulation of medical devices. She has been with Hogan Lovells for 25 years, and she previously served as director of their FDA medical device practice. She has worked on hundreds of FDA submissions, including 510(k), PMA, de novo, IDE, HDE, you name it. She also lectures regularly on medical device issues and serves on multiple advisory boards related to medical device regulation. So welcome to all of the panelists joining us today.

So, a very interesting topic on device description, indications for use, and we heard earlier about the fact that there are many important parts of a 510(k) submission. But, you

know, this area, device description and indications, I've always considered to really be the heart and soul of the submission. And as anybody that's been involved in developing indications for your product and describing your product, you know that it really requires significant care and consideration, particularly as you're compiling that regulatory submission.

What you say your product does and how you describe where and how your product will be used are not only important details, but certainly are the result of a lot of strategic regulatory and even business decisions, because they'll not only define what it will take to get your product cleared or approved, but they'll also dictate -- or that will also dictate marketing claims for your product, competitive considerations, certainly quality design control requirements, risk management, and reimbursement strategy. So definitely, very, very critical elements that require great care and consideration.

So, to kick us off, I have some questions here. Kelly, I wondered if you could kick us off with just your thoughts about considerations that a manufacturer should weigh when they are writing that indication for use and intended use, just how general or how specific that should really be. And you might need to put your mic on.

DR. BAKER: Okay.

MS. STAROWICZ: There you go.

DR. BAKER: Yeah.

MS. STAROWICZ: Great.

DR. BAKER: Thank you, Sharon. Yeah, thanks for inviting me here today, I really appreciate it. I'm actually very excited to talk about this. I really love writing and I really love technical information, so putting that all together in a 510(k), I think, is very -- it's actually kind of fun.

So I think what Aakash and -- both Aakash and Vikansha mentioned about being

simple and consider those things when you're preparing a submission, I think they also apply to the indications. So, the first thing you should do is really just determine which predicate devices are comparable to your device in terms of the design, intended use, and performance. A lot of times these things are a little bit different, and we need to really carefully analyze and compare them across devices.

The most recently cleared devices will represent FDA's most current thinking, and so those really should kind of weigh more when you're considering those various predicate devices. And actually, the device or devices with the most desired and relevant indications should be considered primary, and you kind of operate off of that.

Additional predicates can be used, but I've often found that when people try to kind of include multiple predicates, they don't really add value and they can actually be cumbersome. If specific features are needed, additional predicates for comparison, additional predicates can be used, but I would resist the urge to include multiple predicates and focus on the most relevant.

Another thing is the distinction between indications, which I think of as which patients, and intended use is sort of how they're used in surgery, can be blurred in some of the predicate indications. And that does create a little confusion when you're trying to consider well, what should I do? You know, I have these older things or I even have this thing that says something different than what I might see on a more recent submission, clearance.

So for example, indications may include spinal levels and the number of levels, which is really an intended use, but personally, actually some of these intended uses being built in through the indications are kind of nice because it leaves no room for interpretation by users and people in the field or surgeons, if they're wondering what the indications are when we try to promote these devices.

In addition to the predicate information, you may use -- but I believe Vikansha mentioned this, you may use additional information such as published literature, clinical data, but again it really depends on FDA's current thinking on the specific device type.

The one thing that I feel that even if you have some variations in your indications, FDA is always willing to work with you. Sometimes it's just a matter of tweaking a couple of words. I do believe that we've been getting better -- "we" as industry and FDA together have been getting better at being more clear and not having these complex indications, but they're still out there because the devices are still out there, so yeah. So that's --

MS. STAROWICZ: Great. No, great. Thanks, great reflections there. And I guess, Glenn, building upon the predicate device question, you know, what happens? What does a manufacturer do when their indications for use do not completely align verbatim with a predicate device? So, what would be your suggestion or recommendation for how that should be addressed in a submission? And I actually have a part two to that question, but I'll let you answer this first.

MR. STIEGMAN: Yeah, thanks. Thanks, Sharon. So, when they don't align, the indications that is, there are sort of two scenarios that you would have to look into. One, what's not aligning? Is it clearly just a different device altogether or a different indication, we are trying to fit a square peg into a round hole just to get through the 510(k) pathway? You know, we do see that a lot, and thankfully for the de novo pathway, we're able to have sort of an outlet to push these devices, depending on the risk profile, into a viable pathway to market.

The second scenario is where you're just trying to combine a multitude of different indications. We're seeing devices that have a lot of different functionalities where, you know, back in the day their intended use was singular, and nowadays, they're coming in with multiple intended use or indications. And I think it's clarity -- and I think Caroline hit

this on the head, it's the communication, it's the clarity, it's trying to keep it simple, and it's how you describe your device. If you're able to communicate effectively with why and how your device is able to treat the patients and how that lines up with the predicate, then things should go relatively smoothly.

MS. STAROWICZ: Great, great. And actually, my part two was really around also in a similar vein for predicate devices. As we know in orthopedics, we have many older predicate devices, and we know this has become a bit of a hot topic in recent years. And I've seen statistics around 20 percent of 510(k)s do use predicate devices that are greater than 10 years old, and I was just wondering if you could offer your -- you know, your reflections on that one as well, and when should an older device be considered as an appropriate predicate device?

MR. STIEGMAN: Yeah. I mean, that's a great question and I have a unique, I guess, experience to have cleared some of those ancient or older devices and then predicating off of those. But, you know, I think we're in a unique therapeutic area in spine because a lot of those legacy devices, I mean, they are grounded in such simple fundamentals, you know, a titanium alloy pedicle screw system or a PEEK cage. Some of these devices are relatively old, but they've also established a clinical foundation of success; they continue to be used in certain places with great success. So, when you're building off those sort of older predicates, certainly they can be used from a performance standpoint, indication standpoint, because they're still relevant.

I think where you get in trouble is where you get to the outdated technologies, and you're trying to leverage components or functions or design features that may have fallen out of favor, and usually that's because of safety or difficulty or effectiveness surgeons were seeing. But I think, in many cases, we've had to use older technologies, but they are essentially the same from a performance, indication, and utility standpoint.

MS. STAROWICZ: Still considered state of the art in many cases, yes.

MR. STIEGMAN: Correct.

MS. STAROWICZ: Great. Pivoting a little bit to you, Janice, you know, we hear a lot about compatibility issues with devices, and as the complexity of devices grows and as manufacturers might be submitting 510(k)s for different components that would be compatible with not only their own devices but even compatible perhaps with even competitive devices, I was wondering if you could offer some thoughts about how a manufacturer should approach this topic in their submissions.

MS. HOGAN: Yes, we see this to an increasing degree in submissions these days in orthopedics, but also in other areas. And so, clients will often ask and -- say I make Device A, but that can be used with somebody else's Device B and a Device C. What do I need to do? And I usually start by saying there are two ways to deal with compatibility: You can either try to do it generically and say my device is compatible with things that meet these criteria, or you can do it more specifically and try to name what would be compatible.

Whichever way you choose to do it, you have to obviously have the test data to back it up, and FDA sometimes will now ask us more questions about this. I would defer to the FDA folks that say there seems to be increasing knowledge and interest in this just as a general interoperability type of consideration and thinking about how different devices fit together that may or may not have been designed to work together.

And another thing I always encourage clients to do is, before you're going to do that, if you're going to enumerate specific devices are compatible, make sure you read the labeling with a fine-tooth comb and ensure there's nothing that would conflict with your effort to say these things are compatible, and really go over it line by line and make sure there are no contraindications or warnings that would not make sense for -- together with your own labeling.

There can be other issues, too, like liability -- maybe Company B doesn't want you saying your device is compatible with theirs -- that doesn't directly impact the 510(k) drafting but still has to be considered.

MS. STAROWICZ: I imagine just even sheer design controls for postmarket changes, too, might get a little tricky if you're dealing with compatibility with a competitive product.

MS. HOGAN: Sure.

MS. STAROWICZ: Kelly, Aakash mentioned in his presentation some circumstances where manufacturers might consider bundling 510(k) submissions. Have you had experience in that, and when do you think it makes sense for a manufacturer to actually consider taking that route?

DR. BAKER: Yeah, so bundling can be really -- you know, can be very effective and efficient putting a number of devices into one submission rather than multiple submissions, but it can also create a lot of confusion; it can create utter confusion with the reviewer if it's not presented right. So actually, Aakash presented -- he did talk about the bundling guidance today, which I think is really helpful. My take is that it really makes sense to bundle these devices within a single 510(k) when they have the same product code, the same material change, the same design change or something, you know, something that's the same across devices.

It may also make sense when you have to make changes to multiple devices in the same product family, and that's the other thing that I think we're also -- you know, as companies get larger, they add more product lines to their portfolio, you can end up with a lot of cross-devices or very similar things where you need to apply something across the board. Such an example would be HA-coated devices or 3-D printing or market compatibility, maybe, for the same or even similar product code.

But as FDA mentioned, I would say to ask them when not sure because it really

benefits. If they know it's coming in and you can say, hey, this is the approach we'd like to take, and if they say that we would like you to take another approach, then you can sort of adjust your plan and decide how you want to submit. The one thing that would be really important in these bundled submissions is to be 100 percent clear about the scope and then justify why you think it's appropriate to bundle them.

The other thing that I've experienced is when submitted -- when we submit, we would submit similar devices or related devices, but they were not bundled. At the same time, that can cause confusion as well, because they may be sharing some of the same supportive information, so there's sort of a balance between those two things. Of course, what you don't want is FDA to come back and unbundle something and take something out and requiring you to submit something, so that's why you really need to be careful about how you're considering it. And again, it all comes back to being clear and concise and making sure it's clear why they should be together. And images, some kinds of tables, things like that can be very helpful to orient the reviewer to what you're looking to bundle and include in your submission.

MS. STAROWICZ: Great. Great considerations.

Kind of in the spirit of also incremental design changes, Glenn, if I might ask you, Aakash also covered -- you know, he spoke about incremental design changes that may ultimately trigger the need for a new 510(k) and how manufacturers should be considering not only that trigger change but all of the accumulative -- the impact of the chief changes leading up to that on safety and effectiveness against the device described in that baseline submission. So, in your experience, what are some best practices for manufacturers to consider for doing this? And are there any watch-outs?

(No response.)

MS. STAROWICZ: I think you're muted.

MR. STIEGMAN: Yeah, yeah. Yeah, I think the one thing that we look at, and plunking the new client that has a new device that has yet to reach the market and they were developing the 510(k), is really where do you want to be in 5 years or 10 years with this device? And depending on their answer -- meaning they could say, oh, we want to add this functionality, we want to do this with it, we want to add this coating or make these claims -- it really allows us to establish the proper strategy for introducing that particular device to the market.

And whether it's a phased approach and we send in the bare basic type of device and totally start to incrementally change that device through the 510(k) process, it allows us to strategically plan that out but also communicate effectively with the FDA on what the overall plan is. In a lot of circumstances, that's not the scenario. They see a device, they want to make some changes to it, and then we have to decide well, is that a letter-to-file type change or is that a special 510(k) or maybe even a traditional type change?

And we really just turn to "When to Submit a 510(k) Guidance." I mean, I think that's been one of the most frequently used guidances at MCRA because we are approached so often with hey, we want to make this change and we don't want to get in trouble, so what is the best pathway to go forward? And what I think we -- you know, our track record is pretty good with establishing what should be a letter-to-file and what should not be and submit it.

You know, I think in general, one thing that we have seen is you're depending on the company and where they are within the development process and where they are with being acquired or whatever. Sometimes we'll take a very conservative approach on making these changes. We've seen in the past when a company is about to be acquired and there are a substantial amount of letter-to-files that they want those actually vetted through the FDA and sent to them so the FDA gives their thumbs up of approval or clearance of those

changes.

The scenarios that are troubling is when they engage a client and they do have a whole desk full of letter-to-files that clearly should've been submitted to the FDA, and how do we communicate effectively to the FDA why those were not submitted and what plan of action should we engage the FDA to get those clearances properly through the FDA review cycle? Many of these cases are because of some negative outcome or safety outcome, but still, it really takes communication. It takes being sort of clear and concise in how you really go through this process, and communicate with the FDA on these changes and why they're occurring and why you're making them, whether it's surgeon preference, just evolution of the device, or maybe even a safety issue.

MS. STAROWICZ: Thank you.

I'm going to keep things moving along here in the time we have remaining. Janice, I wanted to get your thoughts around clinical data in a 510(k). And assuming a company has, say, obtained clearance or approval outside the United States first, and there may be significant amount of clinical data either through clinical studies or real-world data or real-world evidence, are there any circumstances, from your perspective, where it would be appropriate for that company to include that proactively in a submission even if it's not been asked by -- for FDA?

MS. HOGAN Right. So, I'll give an illustrative example from a 510(k) I'm working on right now that we're preparing to file. We had a pre-submission meeting with the FDA; the FDA told us that they agreed with us that the primary basis for our submission should be animal data and that we did not need clinical data. And so, in that case, it's just as you said: We have real-world evidence, and we have complaint history from outside the United States which looks good, so we are going to write briefly into the 510(k).

First and foremost, you have to meet the truthfulness and accuracy requirement, so

that's the floor, and we must disclose what's relevant. And so, in my practice, we will usually advise clients based on that. If you have information that's relevant, you should provide it. It does not mean that you need to write an extensive clinical report if FDA has said it's not required. And so that's the way I usually advise people.

On the other hand, suppose you knew that clinical data was not required, but you had a significant adverse event. I would advise people that they would have to disclose the foreign experience if it's relevant to safety.

MS. STAROWICZ: Okay, great.

Kelly, one quick, hopefully quick question to you, and then the remaining time we'll open it up to any final thoughts from all the panelists. But, you know, we heard a bit about a requirement for device-specific instruments being included in a submission and the type of information that FDA would be looking for in that, but if a manufacturer wishes to introduce maybe a new device-specific instrument for the same system that was not previously provided, information was not provided in the prior 510(k), what's your thought about requirement for submitting a new 510(k), just for the addition of that instrument? And you're on mute, too.

DR. BAKER: Thank you. Yeah, obviously FDA would have to comment on this specifically, but I think it's a little complex because it depends on the nature of the instrument, and it does, again, come down to risk-based approach in terms of deciding when to submit. Something that was really specialized, like there's some specialized instruments such as vertebroplasty instruments, Kinex delivery, navigation instruments that require -- it may require submission due to the risks associated with their use. FDA may need to look at the patient-contacting materials, the cleaning, sterilization, usability, actual performance. But that would be very specific to those types of instruments.

For other instruments that don't present new risks compared to existing instruments

or do not present new patient-contacting materials -- because, again, FDA needs to review that -- it may be appropriate to internally document only. But I would say, when in doubt, it's best to err on the side of caution. You can always ask FDA. As you know, they are open to these questions from us, so they'd rather have us ask and find out ahead of time rather than just take an approach that ends up being inappropriate, so that would be my advice.

MS. STAROWICZ: Okay, great. Thank you, thank you.

And I see we only have about six minutes left to the session, so I think in the time we have remaining I just really wanted to open this up to all of you and ask if you have any concluding remarks or any final tips or words of wisdom for companies as they're approaching the topic of device description and indications for use.

Glenn, let me start with you.

MR. STIEGMAN: Yeah, I think it boils down to transparency and communication. I think you hear that message throughout the FDA's presentations, and I think that bodes well with success, especially for our clients. You know, when we communicate with FDA, we describe the devices, we describe the clinical scenarios in which they're being used, and then we're able to work together through more effective 510(k)s.

You know, a lot of our companies and clients, they've been developing -- and I'm sure Janice and others see the same thing where they've been developing these devices for years and years, and it's like their baby, and the only thing they want to do is show off their baby, how good it is, how smart it is, how much better it is. And we really have to hone that in to really be a part of the 510(k), some things on the equivalent pathway, and just develop the right indications, the right descriptions, and show how it matches. And hopefully, the FDA is able to ask the appropriate questions, and the client has the -- or the company has the appropriate data to substantiate everything.

MS. STAROWICZ: Great. Great, thank you.

Janice, your thoughts.

MS. HOGAN: Some things that I've learned over the years, you know, having every week reviewing a couple of 510(k)s or working on drafts of several 510(k)s, as part of my mental checklist of things, I always look at the company's website and compare against the device description in the 510(k), particularly right before we file, especially if you have different claims that you're allowed to make outside the United States versus inside the United States. It is all too common that right before we file a 510(k), we find many things in the company's website that needs fixed. Either we need to update the device description, or we need to update the website because it's not in alignment. So that's one thing.

I would suggest that -- maybe everyone does this already, but if you have an international website, it can be complicated to keep everything in order to meet U.S. requirements and foreign requirements, so that's something I would recommend everyone do.

And of course, the refuse-to-accept checklist, as much as people moan and groan about it, I think that it has been helpful and hopefully has improved the quality of 510(k)s for the FDA's sake. I think it makes it a lot more clear, and so small issues that used to sometimes slip through the cracks like colorants, now we're much more attuned to making sure all those kinds of things are addressed. And videos, I think, can be very helpful to include along with the 510(k), especially if there's anything new about an operative procedure. So those would be my comments.

MS. STAROWICZ: Any of those models and all of those things. Any way to fully illustrate how the product is used. Great. Great points.

And, Kelly, we'll leave it to you to conclude with your thoughts.

DR. BAKER: Yeah, I was actually planning to talk a little bit about some of the -- you know, this complex information and kind of making it simple because that's one of my

things that I personally feel is really important, is being clear and concise. I follow the "simple is always better" approach, and I think what manufacturers should consider when they're preparing their 510(k)s is that -- who's looking at this on the other side?

Sometimes we get really involved in our projects and we -- yeah, like Glenn said, we want to talk all about it because they're so great. But really, the reviewer needs to understand everything, and we have to have a complete and thorough and concise story and try to -- you know, these can be -- as we talked about bundling, these can be extremely complex submissions with a lot of information, and if we want to have FDA review it in a timely manner and be able to absorb everything that's there, we need to present it in a clean and consistent manner. So, I think that is a very important part and to consider how that might be seen.

I like to tell my regulatory team when everything seems daunting, I say, if it were easy, anyone could do it. But today, I want to tell manufacturers that it is -- you can do it; you just need to be thoughtful and deliberate about making your submission clear and concise and consistent, and consider who's going to be looking at it and try to give them the information in a way that's most helpful to them. It will help everybody in the long run.

MS. STAROWICZ: Great. That's a perfect ending to this wonderful session. Many thanks to Janice and Kelly and Glenn for joining us, really packed a lot of insightful information and tips and things for all of us to consider. So, all of these activities have a direct impact, of course, not only on the premarket activities but certainly postmarket, as well. So many thanks, and I really appreciate the great discussion today. Thank you.

So, I think right now, this part of the agenda moves us into a general Q&A session, and I wanted to be able to introduce our moderators for this, Colin O'Neill, who I already introduced to you, and Ronald Jean and Brent Showalter.

And just by way of introduction, I will start with Brent. Brent obtained his doctorate

in bioengineering at the University of Pennsylvania after completing his bachelor's in mechanical engineering at Brigham Young University. He has been at the FDA for five years and is currently an acting assistant director in the Division of Spine Devices within the Office of Orthopedic Devices.

And also, we are joined by Ron Jean. Ronald Jean obtained his Doctor of Philosophy degree in biomedical engineering from the Johns Hopkins University in 2004. He has been at the FDA for nearly 16 years and is currently the director of the Division of Spinal Devices within the Office of Orthopedic Devices.

So this will be a great opportunity. I hope you've received lots and lots of questions through the e-mail box, but I wonder if I might be able to start with one question in particular for -- just to kind of get the ball rolling, if I may. So it really picks up on where we left off on the topic of device compatibility that Janice Hogan spoke a little bit about, particularly for devices that are intended to be used with other devices, again, either -- it can be either from the same manufacturer or different manufacturers. And I was just curious to get FDA's perspective on what you think would be important to be included in submissions of this type since it seems to be growing in prevalence.

DR. JEAN: Sure, thank you for that question, Sharon.

You know, I think that was a really good point because there are different scenarios. So, there are certain devices within spine that are intended by nature to interact with other devices, for example, we have cerclage fixation devices that actually are indicated to be used with any rod of a similar material. So that's a very easy scenario. But a lot of times we have inquiries about trying to use a particular screw design with another competitor's rod or trying to combine different products for use together, and so I would say it really depends.

The minimum expectation when we can actually allow a company to move forward

and combine their device technologies -- for example, I can cite one of the first few growing rod technologies had an agreement with a competitor to use their actual fixation screws. At a minimum, we would want some type of documentation of an agreement between the two firms so that they would notify each other of design changes because that could impact device performance.

And then depending on the case, we may want to see actual performance data related to the range of scenarios that, that compatibility would extend to, for example, testing of Company A's screws with Company B's rods, or if they're going for a much more generic set, you know, a vast array of testing.

And another good example I can bring up are the pedicle screw guides. So we've seen, with pedicle screw guides, those systems evolved to having a very limited number of scenarios under which it could be used with maybe one or two pedicle screw systems, and the company was able to then move further and expand that to a few different additional pedicle screw systems, and then ultimately, the company was able to provide performance data that demonstrated to us that they could be used for any pedicle screw system meeting certain defined criteria. So, I would say it really starts again with the company actually having an agreement with the other firm which they want to have some type of compatibility with, and then providing that performance data as appropriate.

MS. STAROWICZ: Great, thank you. Thank you very much. I'm going to turn it over to you guys. I know you -- I'm sure you have many questions that have come in. Thank you.

DR. JEAN: Sure. And before we jump in, I'll just take the prerogative and add one more thing. I think Janice brought up a really good point about the fact that, you know, sometimes they look through the websites during their interaction with a client to sort of make sure everything's in alignment with the submission. And what I would highlight is that within OHT6: Office of Orthopedic Devices, we've now been within a TPLC structure for

over a year, and over two years if you count our pilot phase, and during that time our reviewers have become a lot more accustomed to conducting what may be considered a TPLC, or total product life-cycle, review.

So we do look at adverse events, and we try to feed that information for either the particular product or the product class back into our reviews to make sure that the current submission at hand is actually addressing all known issues that we're aware of.

We also look at recalls, and I think our reviewers are also getting better at looking for claims and screening for any materials that could cause problems for the firm down the road, and we definitely try to work with the 510(k) submitter to make sure that we remove anything that maybe is an unsubstantiated claim or material that isn't pertinent to the 510(k) substantial equivalence determination. But I do think that was an important point to highlight since, traditionally, going back more than a couple of years, we were segmented into premarket/postmarketing plans/functions, whereas now, we actually consider the full gamut even within our premarket review.

MS. STAROWICZ: Great, thank you. Thanks for addressing that, Ronald.

MR. O'NEILL: So, I can take one of the questions that we received in the mailbox to kick it off. You know, there seemed to be a lot of excitement about the eSTAR program and we got a very simple question: Where do I find information using eSTAR? So, to answer that question best and to maybe provide a little bit of more current information about eSTAR, I'd like Zane Wyatt to join to give an answer to that question and a few additional comments.

DR. WYATT: Hey, Colin. Thanks so much. Can you hear me all right?

MR. O'NEILL: Yeah, thank you.

DR. WYATT: All right. Yeah, so basically how it's working right now is the FDA has a 510(k) pilot's website, and this 510(k) pilot's website has information on all of our current

ongoing pilots, whether they are the quality in review pilot or whether it's the eSTAR pilot. There were a lot of questions you were mentioning about how to get into it, the pilot, or how to use eSTAR. All of that information is on that website, including a link to the actual eSTAR tool. It's a smart PDF, so it's just a simple PDF document that you download from the FDA web page.

That being said, all of our -- both our current pilot and the upcoming summertime pilot are both completely enrolled, completely full, but that's why we wanted to make a real big point here that you don't have to be in the pilot to use eSTAR. Anybody is welcome to use it now for submissions starting tomorrow. The only difference would be is in the pilot you get excluded from RTA and you have a couple other sort of, you know, special permission style things.

But even if you aren't part of the pilot and you choose to use eSTAR to submit your submission, you'll get a proactive reach-out from our team, you'll get a lot of handholding, you'll get a lot of support from our team. So even if you're not in the pilot, just the fact that you're using the tool generates a lot of excitement from us, and you'll get a lot of interaction with us on that end. So, we definitely recommend, people, you don't wait for a pilot to come up again for you to enroll. If you want to use it, use it now, and you can get all the information about how to use it, what it's designed to do, what programs it's designed to work with, all that stuff is going to be on the FDA pilot's webpage. It's kind of a long link, so it's hard to just spurt it out, but if you Google like FDA 510(k) pilots eSTAR, it will be the first link, it will be the first hit. And it's really easy on the webpage to find what you need to know.

And then, yeah, if you do have any particular questions about using it or using it to construct a submission or hey, I'm not in the pilot so I am actually still -- I have to abide by eCopy rules, so how do I make my eSTAR, make sure it gets through eCopy? Instructions

are built into eSTAR on how to do that, but if you still have further questions or you run into issues, you're more than welcome to reach out to the eSTAR mailbox that was linked in my presentation.

It's also going to be that eSub pilot mailbox. That's the one you're going to just send a message to that inbox, and we'll be happy to answer it and help guide you to make sure you both pass eSTAR. It has built-in validation, so it will make sure that you have a complete eSTAR that's ready to submit and then also give you instructions on how to package it properly: the correct folder structure, the correct hierarchy, how to build your USB drive, all that sort of stuff to make sure it gets past the eCopy hurdles. Because, like I said, you're not going to get that -- like those exemptions that you would get if you were part of the pilot, but you'll still -- you are allowed to use it for a final submission, and we want to stress that and encourage people to do that.

MR. O'NEILL: Thank you for that, Zane, and I think we're all excited for more people to use eSTAR --

DR. WYATT: So are we.

MR. O'NEILL: -- in the future.

DR. SHOWALTER: Yeah, sure. All right, I'm going to take the next round of questions, so this individual submitted: Under the new criteria for a special 510(k) qualification, there are two performance data requirements: well-established methods and review of data under summary or risk analysis format, and the chemical performance testing per ASTM F2077 and ASTM F2267 for intervertebral body fusion devices. FDA-recognized consensus standards certainly qualify as well-established methods, but the specific question is, can mechanical performance data obtained through ASTM F2077 and ASTM F2267 testing for intervertebral body fusion devices be reviewed in a summary or risk analysis format, thus meeting that particular criterion for a special 510(k) submission?

So the answer to that is a typical government response of "it depends," so let me tell you a little bit about what it depends on. So if the subject cage is a minor design modification, so there's some existing cleared product and you're tweaking something a little bit, and the performance testing that you're conducting is essentially repeating testing to confirm that it does not establish a new worst case, in that case, the testing may appropriately be summarized, and also in accordance with that, a special 510(k) may be appropriate.

However, if you're doing a full battery of testing, even though you're using consensus standards that are very well established, we look at a lot of different elements of the test report, and in particular, we look at -- well, in addition to the numbers that can be summarized very well and averages and things of that nature, we look at load displacement curves and failure mode pictures. So those are elements of the test report that are very difficult to summarize, and for those reasons, we typically ask for a full test report and request a traditional 510(k).

MR. O'NEILL: Ron, I think you're still on mute.

DR. JEAN: Yeah, Colin, would you like to lead us off with the next question?

MR. O'NEILL: Yeah, yeah. So we got a question about the RTA addendum: How common is it to receive an addendum with your RTA response? Is this a trend towards more feedback up front?

So, I would say there's an addendum attached to RTA responses in the minority of cases. There is a trend towards wanting to provide more feedback up front. As the reviewer looks through the submission, if any elements that would be raised in the substantive review phase that are not part of the RTA criteria, if there's time for the reviewer to collate some of that information and put it into the addendum, then it will be done. And that type of information runs the gambit of, you know, information that might

be significant in holding up a positive pathway forward or something very minor that the RTA checklist does not cover.

So, this is something we try to encourage everybody to do. This is just another mechanism, in addition to interactive review, just to start the conversation and make sure that all the right information is provided up front and industry gets a heads up on what we're looking for potentially in their submission.

DR. JEAN: Thanks, Colin.

So, another question that we received is two parts, and so the first part is: For pedicle screw systems, we typically list the subject components -- PGA screws, rods, connectors -- in the body of the 510(k) for the sample table of components from FDA and the previously cleared components in the appendix. Is that appropriate? Would another format make the review easier? And the subpart to this says: Should the table include a list of each individual part number, or is a format like 76-04XX and then the range of sizes preferable, which represents 4 mm diameter, 30 to 65 mm links?

So, stepping back, I think for ease of review, it's best to have all of the information in one place, so to sort of catalog all of your products, and you can mark up in the same table, for example, what's been cleared versus what has not been. You know, really there's a need in a general sense to identify all products that are part of the system and all products that would interact with the changes being made.

The comment that I have related to the part number format is I think it's perfectly acceptable to have that type of style, but you do need to define what that product identifier represents. For example, here it was spelled out what the representation was for the 04 and presumably the XX would be the length of the screw in question, but 76 would need to be identified. Is that just the screw type? Is that one of the product listings? What is the importance of that number? So as long as you have some type of legend that clarifies what

your individual part number represents, that is acceptable instead of listing out explicitly every size range.

The other part of this question is: If we have Class I and Class II instruments for the subject spinal system 510(k), does the FDA want to see a list of the Class I instruments -- for example, the awls, caps -- or just the Class II instruments unique to system implantation?

So, our response to this is, to ensure that there is adequate instructions for use, we would like to know about all accessory instrumentation that is being used with a particular device or device system. But with that said, our focus is really only going to be on those Class II instruments that are device-specific or unique to your device system. It's perfectly acceptable with your Class I instruments to just identify what these are and then get into more detail with the Class II instruments.

So, I thought this was a really good question that's of broad value to the entire audience, and we'll keep on cycling through. So, I'll turn it back over to Brent.

DR. SHOWALTER: All right. Thank you, everyone.

So, the next question is: Which is the current 510(k) guidance for spinal product submission? And then it further clarifies the question by asking what the difference is between the May 2004 guidance for spinal systems and the July 2014 510(k) program guidance for industry.

So I think the main part of this answer is that there are a lot of Center and office-wide guidances related to 510(k) submission, so the second submission that was listed in -- that second guidance document that was listed in that question, the 510(k) program guidance, the full title of that is the "510(k) Program Evaluating Substantial Equivalence and Premarket Notifications." Those kind of guidance documents are broad guidance documents that apply to everyone who is submitting a 510(k) at CDRH, so there are several of these that have been mentioned a couple of times throughout the

presentations this morning. So, we have guidance documents on specials, on bundling, things of that nature.

We also have a couple of spine-specific guidance documents. There's two main ones that I want to highlight. So, the first one was mentioned in the question, the full title of that, I have -- give me just a second to look for the full title of that. But it is just called "Guidance for Industry and FDA Staff: Spinal Systems 510(k)." So, this was published in May 2004, and this is a guidance document that applies primarily to pedicle screw systems and plates. So in this spinal-specific guidance document, that has specific instructions on things like the mechanical testing and the labeling, some sterility questions, those kind of things that are more device-specific that wouldn't necessarily apply to all devices that need to submit a 510(k).

There is a companion document to that -- not really companion, but the counterpart for cages is called the -- it's a specials controls guidance document for intervertebral body fusion devices, and this was published in 2007. And like the general spinal systems guidance document, it has the specific testing, mechanical testing, it has specific things for device description and other considerations for cages. So, I hope that answers your question, and I'll turn it over to Colin to take the next one.

MR. O'NEILL: Yeah. Thanks, Brent.

So, there's a question, you know, I don't -- I guess you could fit in here. Just to let everybody know, there's another Q&A session at 3:15, I believe. If you want your question answered, please get it in as soon as possible. If we get it live during that time, we may not have a chance to read and give a good response.

So, the next question that we received is: If a foreign spine product has a CE mark, can the CE mark submission documentation be used in the 510(k) submission? So actually, there's two parts; I'll answer the first part first.

So the 510(k) pathway paradigm does not take CE mark consideration by itself into the decision making. There are elements that may have been provided to the other regulatory agencies to obtain that CE mark that could be relevant in the 510(k) for our review and other criteria for us to provide a determination of substantial equivalence. You know, we're also aware of new requirements for MDR, MDR Europe, your end requirements for collecting data that can also be very helpful in an SE determination to help decide a substantially equivalent safety and effectiveness profile.

So, the second part of the question is: Are there time limitations for using CE mark documentation in the 510(k) process? For example, if the CE mark was issued 10 to 15 years ago, are that information and testing still acceptable for FDA, or are new ones needed to be obtained?

And again, it's not -- CE mark is not technically part of the substantial equivalence review process. Again, you know, if there's information available that can help support a predicate comparison or mechanical testing or available real-world evidence on that device that has a CE mark, that would certainly likely foster that predicate comparison and an eventual, hopeful, positive outcome in that -- so with that, I think I'll turn it over to Ron for the next question.

DR. JEAN: Okay. So, our next question is: In relation to the indications for use statement, what information is FDA looking for when there are differences in the indications compared to the primary predicate device?

And so before jumping into this question, I do want to go back to something that Glenn mentioned during the industry panel. Again, there's a difference between intended use and indications for use and intended use may potentially -- a difference in that may potentially kick you off the 510(k) pathway and align you down a de novo pathway if you meet that program's specific criteria. But in terms of indications for use, I would say in

general, you're usually looking at performance data request if you're going outside of those boundaries.

But in the very simplest cases, when there is difference in language between the primary predicate device and it does not change the intended use, it does not change the indications for use or the patient populations that you're targeting, then you have a few different options. You can potentially just walk through in your submission those deviations and explain how you believe you are still substantially equivalent.

Another thing that we've seen companies do, and you don't always need to bring in an additional predicate or an additional predicate device, is have a primary predicate that walks you all the way down the flowchart, but perhaps there's language that may be very similar that you flag to us by citing this additional predicate device. So that's also an option that you can do. You don't have to do that. You can always provide a line-by-line or word-by-word comparison of the deviations, and we'll be happy to look at that in the submission, but again, it really does depend on the degree of change and variation there is.

And I will turn things over to Brent.

MR. O'NEILL: Looks like we have a few questions that pertain to information that we present this afternoon. Some of the questions will be answered, I think, in the presentations and we can fill in the gaps, I think, in the next Q&A session.

Were there any other questions that would be appropriate to go over now?

(No response.)

MR. O'NEILL: Guess not. Okay, I'll send it back over to Sharon, thank you.

MS. STAROWICZ: Thank you very much, gentlemen.

We now turn our attention back to another opportunity for audience participation, and I'll turn this back over to you, Brent, to get it started.

DR. SHOWALTER: I thank you. So, I realize it's a little bit dangerous, I think this is

the last thing before lunch, so we're asking for audience participation right before lunchtime, so we very much appreciate everyone who sticks around and answers these questions. We have some good questions lined up for you and looking forward to your help with this.

So, there are two ways to provide feedback to us. You will see a slide with a QR code and you can -- this is Survey Number 2, so you can take a picture with your iPhone and it will take you to the website. You can also go to the menti.com website and type in the digital code 18-62-70, and you'll be able to put in your responses to the questions on that site.

So, with that, I believe we can move on to the first question. And the first question is: Does your company share feedback from the FDA with other companies or in a trade group to proactively avoid issues with your 510(k) submission?

So, I'm looking, we're starting to get a few responses in, and there's a few more skewed towards the no side than the yes, although it's pretty even right now, so we have about a 50/50 split between people who share their information with other companies and those who do not. So, we'll give it just a few more seconds for that to stabilize and I'll move on to the next question. It's looking pretty consistent. So, we have slightly more people -- as more respondents come in, it's skewing more towards no. So, we probably have almost two-thirds of the group that says they don't share their information with other companies and about a third, give or take, do. All right. Well, thank you to that and we'll move on to the next question.

So, this one asks: How many of you have forgotten to describe all of the proposed changes in the device description or executive summary of your 510(k) submission?

We'll give a little bit of time for answers to start coming in. The first initial cohort, it looks like it's heavily skewed towards no, 70 percent or so saying that they don't forget

these elements. There we go. As more answers come in, we're now at about 79 percent saying that they don't forget these elements and about 20 to 25 percent saying that they do forget it. Well, thank you for that, and hopefully the presentations will help provide information to avoid that in the future.

I think we can move on to the next slide. So, this one has multiple choices for answers: So how often do you include detailed descriptions and figures showing how subcomponents interact? So, the answers here are never, sometimes, frequently, and always. And I apologize, I may have been going a little bit quickly for the first question, so we'll give you a little bit more time to respond.

So as the answers come in, it seems like the frequently group is the most common, but there's definitely a spread throughout all four answers.

And frequently is still the most common answer to describing the detailed descriptions and subcomponents.

While the answers are coming in, I'll take the time to say talking about the subcomponents is very helpful for us. We're able to see especially how key components interact with one another. That helps significantly in understanding how the device works and in going through the submission.

Well, it looks like the answers have stabilized, so we have 38 percent at frequently, 34 percent at sometimes, 22 percent on always, and 6 percent say never. All right, so I think we can move on to the next question.

So, this is a more straightforward question. So, this is -- it says: Assuming it's applicable to the device, is the phrase "for patients with degenerative scoliosis" appropriate to include in the indications for use? And the answers are -- the possibilities are yes or no.

And for some reason, I'm not seeing the responses come in. I see people answering, but I don't see what the answers are, so I don't know what you guys are quite thinking yet,

but hopefully that will change in a minute.

It looks like we've had a number of people respond, but I apologize, I don't have an answer for you yet. In a second here, we'll give it one more second to show up, and if it doesn't, I'll kind of explain the answer that we're looking for and then we'll move on.

So, what we're particularly looking for in this is, this is a phrase that would be appropriate to include in the indications for use because it describes the group of individuals who would be needing the treatment for this. So thank you for -- I'll assume the 50 people who responded said yes. All right, if we could move on to the next question.

This is a similar phrased question, so it says: Assuming it's applicable to the device, is the phrase "made from titanium alloy" appropriate to include in the indications for use?

All right, on this one the answers are showing up, so thank you to whoever fixed that. We're at about 10 people responding so far, and of those first 10, about 80 percent are saying that it is not appropriate to include, and the other 20 percent are saying yes.

All right. The answers are still coming in, and no is the -- still a number of people that are saying no compared to yes. All right, so as most people were indicated, just because this -- "made from titanium alloy" is a phrase that describes the device, it isn't really describing who would be treated or who would need the device, and so because of that, this is not an appropriate phrase to include in the indications for use, generally.

Now, there may be some situations in which it's appropriate to include a material, so we have seen some cases where the material affects what kind of groups or individuals who'll be treated by it. So, in that case, it is appropriate to list the material, but in most situations using -- listing a standard material like titanium or PEEK is probably not necessary. All right, can we move on to the next question?

So, this is an open-ended question, so it says: Do you have any feedback for OHT6 in our review of your device description and indications for use in 510(k) submissions?

The first answer in says, not in particular, none. We'll take that to mean that things are going perfectly and -- no, we always appreciate your feedback, and if there's anything that we can improve on, we like to hear it. Thank you.

So, right now, the answers are leaning towards not at this time; recent feedback we've been given is generally on point. And this type of question might be easier to answer through our e-mail, e-mail address that has been mentioned a few times throughout the submission. So we'll -- as has been mentioned, we've got this e-mail box and e-mail address we're going through in listing the questions we can answer now, and there will be some that we'll be trying to answer at a later date, so we will be looking at all e-mail even if we don't have time to get to them today.

So, one of the questions was: Define the term "appropriate" as it pertains to use of statements for intended use.

So, this is a very broad question but very good. I think a general guideline would be to indications for use or intended use should define the patient population that the device is trying to treat, okay? And for more specific feedback, I believe the slides for the presentation on indications for use will be made available later.

We're getting a feedback to keep this type of training going. All right. So, thank you very much for these, we'll -- I apologize. Near the end, we're starting to get a few that haven't been answered yet, but in the interest of time, I'm going to move on. We'll try and answer your questions in a little while. So, if we could move on to the next slide?

Never mind, that was the last one, so I guess I do have a little bit of time. Would it be possible to go back and see the Mentimeter questions and we'll try and get a few more? The slide after this, the open-ended responses.

So, I believe one of the questions were about differences between feedback a competitor receives versus another. So, I think that's something that we're always trying to

pay attention to. It's a little bit difficult when we have 20 people within the Division of Spinal Devices looking at everything, and we do our very best to be consistent. But going back to a theme that's come up several times in the panel is, if there is something that is significantly different, please bring it up with the lead reviewer and we'll talk about it, and maybe there's something about the situation that we didn't quite understand or grasp that first time.

All right, so I believe with that, now we are ready to move on to the next portion, wrapping up the spinal session. So, thank you to everyone who has submitted questions.

MS. STAROWICZ: Great. Thanks so much, Brent, excellent. And my thanks to all the presenters in the morning session, again to you, the audience, for your engagement. And there's certainly been a lot of information to digest, so I think it's the perfect time for us to take a lunch break at this point.

So, we're going to break for about an hour, and we would just ask everybody to be back at 12:30 for the kickoff of the afternoon session. Again, just a reminder, it's a great time to please continue to submit your questions to the FDA mailbox, and hopefully those can be covered in the latter Q&A sessions. And bon appétit, we'll see you back at 12:30.

(Whereupon, at 11:27 a.m., a lunch recess was taken.)

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A F T E R N O O N S E S S I O N

(12:30 p.m.)

MS. STAROWICZ: Welcome back from lunch, everybody. I hope you all are well nourished and refreshed and ready to tackle the afternoon program. Without further ado, it is my privilege to introduce our next two FDA speakers, Jonathan Peck and Kate Kavlock, who will be presenting on the topic of spinal device mechanical testing.

Jonathan obtained his bachelor's and master's degree in mechanical engineering from Cornell University. He has worked in the orthopedics group at FDA for the last 17 years and is currently a master reviewer in the Extracolumnar Spinal Devices Team. He is FDA's primary liaison to ASTM and ISO for spinal device testing standards.

Katie Kavlock obtained her Ph.D. in biomedical engineering from Virginia Tech in 2009. She's been at the FDA for more than 10 years and is currently the team lead for the Intracolumnar Spinal Devices Team in the Division of Spinal Devices in the Office of Orthopedic Devices.

So, without further ado, I'll turn this over to you, Jonathan, to get us started.

DR. KAVLOCK: Good afternoon. My name is Katherine Kavlock, and I'm the team lead for the Intracolumnar Spinal Devices Team, and I'm presenting today with Jonathan Peck, a master reviewer in the Extracolumnar Spinal Devices Team. We appreciate the opportunity to share with you some of our tips and preferences for conducting and presenting mechanical testing in 510(k) submissions for spinal devices. As an outline of what we'll be covering today, first we'll be talking about the information to include in the performance testing section of your 510(k) submission; then we'll dive into the contents of test reports; and finally, we'll speak briefly about AI responses and a few other considerations.

The main elements of our performance testing section in a 510(k) submission

typically include a description and justification of the test performed; a justification of the worst-case device or devices selected for testing; the acceptance criteria for each test; a summary of results and a comparison to the acceptance criteria; and finally, any conclusions drawn by the tests that support a substantial equivalence determination. Let's start with test selection.

Spinal device tests are typically based on the loading modes, moments, displacements, or angular displacements that a device is expected to endure in vivo. These loading modes can include axial compression, bending, shear, and/or axial rotation. While no single test replicates the complex and highly variable loading scenarios in vivo, the particular tests performed on a device typically take into account the device's placement in or on the spine and the general loading modes that are expected.

For example, interbody fusion devices are tested in axial compression due to their placement between the vertebral bodies. However, pedicle screw systems and anterior plating systems are tested in compression bending due to their offset position from the center of loading in the spine.

Test selection for high-volume device areas is often fairly straightforward. We have several guidance documents, which I'll discuss further on the next slide, that provide recommended testing regimens for many of our most common devices. If you're submitting a 510(k) submission for a device area covered by one of our guidance documents, please consult the relevant guidance and be sure to provide a justification for any test that is recommended that you choose not to perform.

Please also note that certain device features may warrant testing in addition to what is recommended in a guidance document. For example, if a polyaxial screw is designed such that it may be more susceptible to dissociation of the tulip from the screw shank, we often ask for a direct assessment of the strength of that interconnection.

There are three main guidance documents that we'd like to draw your attention to today, as they contain testing recommendations for a large percentage of the spinal device 510(k) submissions we receive. Our guidance on spinal system 510(k)s includes testing recommendations for thoracolumbar pedicle screw systems, posterior cervical screw systems, cervical and thoracolumbar plating systems, and vertebral body replacement devices. Our special controls guidance document on intervertebral body fusion devices contains testing recommendations for cervical and lumbar spinal interbody fusion devices. Finally, last September, we issued a draft guidance for cervical and thoracolumbar spinal plating systems for the safety and performance-based pathway. This guidance document is harmonized with the spinal system 510(k) guidance as far as test recommendations. However, this guidance contains optional acceptance criteria that can be utilized to demonstrate substantial equivalence.

Here we've listed the standard test methods we see most commonly referenced in 510(k) submissions for spinal devices. ASTM F1717 contains test methods for testing pedicle screw and anterior plating system constructs. This allows for the testing of multiple components at once, such as screws, rods, and connectors. ASTM F2706 is similar to ASTM F1717 but includes methods for testing posterior cervical systems with occipital connection mechanisms. ASTM F1798 includes test methods for isolating the interconnections for screw and rod systems. ASTM F2193 has test methods that isolate a single spinal system component such as a screw or a rod or a plate. ASTM F2077 contains methods to test the structural integrity of an intervertebral body fusion device assembly, and these methods are often used to test vertebral body replacements, as well. ASTM F2267 provides test methods to assess the susceptibility of interbody fusion devices to subside into the vertebral endplates.

Please keep in mind that this list is not all inclusive, and there may be additional

standardized tests which may be relevant for spinal devices based on particular device technological characteristics. For example, we often see ASTM F1854 for characterization of metallic plasma-spray coatings on spinal implants.

In addition to our guidance documents and commonly utilized standard test methods, you may be aware that we've recently published articles on the mechanical performance of cervical and lumbar intervertebral body fusion devices. We are seeking to publish additional data on other high-volume product areas, such as thoracolumbar pedicle screw systems. They are devices which incorporate technological features which may require additional characterization with non-standardized test methods.

Similarly, there are devices that are eligible for 510(k) for which no specific guidance documents or standard test methods exist. For these features and devices, the test selection of your submission will likely need to be far more detailed. You will need to provide a justification for the test performed based on the loading modes expected to be endured by the device. In these cases, the 510(k) summaries for predicate devices with similar features or used in a similar manner can provide useful information on how previous devices were evaluated. Please provide a discussion of any literature utilized to justify the testing regimen developed, as well as copies of the literature articles themselves.

Now that you have selected the relevant test to be conducted, it is important that you document your justification for the worst-case devices or construct selected for each test. Selection of the appropriate worst-case devices helps to ensure that all other devices in a system will perform at least as well as the device or construct being tested.

While some test methods will specify an active length, which may drive the selection of the test construct, other methods leave it up to the user to determine the most appropriate device size to be tested.

When providing a worst-case device justification, all relevant device characteristics,

including diameter, length, footprint, height, lordotic angle, et cetera, should be discussed. This may include a discussion of how critical device features, such as lateral windows, scale with device size, or how additive manufacturing parameters impact selection of worst-case components for testing. The most common method to justify a worst case is simply an engineering analysis; using engineering principles to select the smallest diameter screws and rods or the smallest footprint and a vertebral body fusion device is often adequate.

In cases where engineering analysis can't definitively determine a worst case, finite element analysis is often used to simulate loading on several designs to determine which has the worst-case response. We have the most confidence in finite element models performed on single-piece devices. Multiple interacting components can significantly increase the complexity of a model, and it may require more testing to validate the model than would be needed to confirm the worst-case construct or component.

Lastly, initial mechanical testing is useful to help determine worst case. For example, sometimes companies will perform interconnection testing per ASTM F1798 on pedicle screw components to help determine which components may be worst case for their construct testing per ASTM F1717.

Some important additional things to consider for the worst-case determination: The same device or construct can often be determined to be worst case for all loading modes being tested; however, there are instances where the same device may not be worst case for all testing. One example of this is that pedicle screw constructs are often tested with a cross-connector in compression bending, particularly for fatigue, because the connection can create a stress concentration in the rods and lead to earlier failure. However, the cross-connector is often left off the construct for torsion testing, as the cross-connector can increase the torsional stiffness and yield strength of the construct.

Along these same lines, it is important to point out that it may not be possible to

definitively determine a single worst-case device or construct, and therefore multiple devices or constructs may need to be tested under a partial or full battery of testing.

Finally, in general, we recommend that all testing should be conducted on the final finished device. However, you may provide a justification for any differences between the tested device and the final finished device. For example, steam sterilization is not expected to impact the mechanical properties of titanium alloy. Therefore, it is often acceptable to perform mechanical testing on unsterilized metallic devices. If there are differences between the final finished device you intend to market and the device actually tested -- for example, if tests were performed on a prototype -- we recommend that you explain why the results are relevant to the device you intend to market.

Now you know what tests you want to conduct and what devices you want to test. The next part of the performance testing section of your 510(k) submission we'd like to discuss is acceptance criteria. Acceptance criteria should be provided for each relevant parameter for each test. For static tests, acceptance criteria should be provided for yield load and stiffness. For fatigue tests, an acceptance criterion should be provided for runout loads. You may base these acceptance criteria on side-by-side testing of a legally marketed predicate device. Acceptance criteria can also be derived from valid sources of predicate testing in the literature, guidance documents, or in standards. An ISO document is currently being developed with acceptance criteria for interbody fusion devices.

Remember, mechanical tests often do not fully replicate complex physiologic loading environments. Therefore, testing should not be considered to represent a true simulation of in vivo conditions. This is important to consider when determining the acceptance criteria for a mechanical test.

Due to the high variability in physiologic loading scenarios, an effect of the mechanical test may not be accurately replicating physiologic loading. It is often essential

that test results be compared to another similarly-designed device tested in the same manner rather than expected physiologic loads.

Speaking of valid sources of acceptance criteria, I've already shown you published articles on the mechanical performance of cervical and lumbar intervertebral body fusion devices. These papers contain aggregated, de-identified mechanical testing results for interbody fusion devices previously cleared through the 510(k) process. Additionally, the draft safety and performance-based pathway guidance we previously mentioned contains acceptance criteria for cervical and thoracolumbar anterior plating systems.

Each of these documents also contains dimensional range information which may be useful for comparison in the substantial equivalence comparison section of your 510(k) submission to justify that your device falls within the dimensional range of previously-cleared devices. When generating acceptance criteria based on the data published in these papers, be aware of the scope of the papers as well as some of the limitations of the comparisons. For example, some device types were excluded from the analysis presented in the papers. Likewise, the compression shear data presented is only for devices tested at 45 degrees. Note, if a subject device test result falls below the value presented in the paper -- for example, below the fifth percentile -- or if a device feature requires testing in a way not comparable to the published data -- for example, a device tested at 27 degrees in compression shear -- you can always utilize side-by-side testing of a legally marketed predicate device.

Next, we recommend that you provide a summary of your results for each test as compared to your acceptance criteria. This is an example of a fictitious subject anterior cervical plate being compared to the acceptance criteria listed in our draft safety and performance-based pathway guidance for anterior cervical plating systems. It can also be helpful to provide the same tabular comparison of test results in the executive summary

and the substantial equivalence comparison sections of your 510(k). It doesn't hurt to have some redundancy in your 510(k) in this case. However, you may also simply reference the performance testing section of your 510(k) in these other sections.

We want to stress that any irregularities in the data should be discussed in your results summary section. For example, when there is large variability in the data, interpreting the results compared to a predicate device can be challenging. In these cases, additional discussion should be provided regarding the sources of the variability, as well as how the variability impacts confidence in the comparison to the acceptance criteria.

Note that in our draft safety and performance-based pathway guidance for anterior cervical plating systems, we state that a successful result is either one where all test samples meet or exceed the acceptance criteria, or where the calculated average of all test samples meet or exceed the criteria with a standard deviation of less than or equal to 10 percent of the average.

To ensure that the runout load being reported is sufficiently representative of the actual fatigue strength of the device, it is important that fatigue behavior be characterized with adequate precision. ASTM F2077 specifies that precision be established by ensuring that the lowest load that results in a failed construct is not greater than 1.5 times the highest established runout load. For example, if the highest established runout load is 100 newtons, then the lowest load that results in a failed construct shall not be greater than 150 newtons. In ASTM F1717, the lowest load that results in a failed construct should not be greater than 1.25 times the highest established runout load. Additionally, any inconsistencies in the data, such as failure of the device at a load equal to or lower than the load at which runout is achieved, should be addressed.

Finally, in your results summary section, please describe the failure modes observed for each test. Note that not all failure modes are created equal. If testing your device

results in a failure mode that is considered more catastrophic than is commonly seen in predicate testing, we may ask that you identify a predicate with similar or lower test results with an equally catastrophic failure mode. One example of this could be an additively manufactured interbody fusion device that crumbles into many pieces during testing; this failure mode is not considered equivalent to a PEEK device that may experience minor plastic deformation during the same test. Note that cracking extending into the body of a device is almost always considered a test failure. The most notable exception to this is when cracking is isolated to the teeth of an interbody device.

Finally, please provide any conclusions you are drawing from the mechanical testing presented as it relates to the substantial equivalence determination. An example of such conclusions could be the subject plating system performed as well or better than the predicate cited in all relevant comparative parameters, and failure modes between the subject and predicate devices were similar. Therefore, substantial equivalent mechanical performance of the subject device has been demonstrated. As a side note, a similar statement should be included in the performance testing or conclusion section of your 510(k) summary document.

Now I will turn the presentation over to my colleague, Jonathan Peck, to discuss the contents of test reports.

MR. PECK: Good afternoon, everyone. My name is Jonathan Peck. and I'll be discussing some details and preferences that we have for test reports that can greatly aid in our review of 510(k) submissions.

First, we'll be discussing how to appropriately identify the tested devices and provide details regarding construct assembly. Then we'll talk about some considerations for reporting on the apparatus and the procedure, as well as how to report any deviations from a standardized test method. Finally, we'll talk about reporting results, including tables and

plots.

However, before we get into the contents of test reports, we wanted to point out some sources for test-reporting recommendations. Each standard test method contains a reporting section that you should consult for the reporting requirements of that standard. Additionally, our spinal system 510(k) interbody fusion device guidance documents, previously mentioned, also have recommendations for test reports.

However, we really wanted to draw your attention to the reporting section of ASTM F2077, which, in our opinion, is a nice example of the level of detail to provide in a test report, particularly for the description of the apparatus. Updates are planned for the reporting sections of other spinal device testing standards to include similar levels of detail in the future.

One area that can cause -- review of a test report is device identification. Sometimes the name of the device has changed from when it was tested. Please explain in your 510(k) if there are differences in how the device is named in the test reports. Oftentimes, test reports will simply list a vague device or component name and the part number. This can require the reviewer to have to cross-reference all part numbers back to a part listing in order to verify the exact device or components tested. Therefore, in addition to part numbers, please also include the device or component name, materials, and nominal dimensions in your test report.

Finally, please provide representative pretest device images from the most relevant viewpoints, such as from the side, the front, and the top. The images provided should be based on the technological characteristics of the device. For example, you mainly need to provide a single image of a screw; however, it may be necessary to provide multiple images of an interbody device with a plasma spray metallic coating applied to one or more device surfaces.

Often, testing involves not only the test of a single device, but rather the testing of a combination of components or a construct. We recommend that you provide the relevant details as to how the components were assembled to each other as well as to the test blocks. For example, please include tightening torques for screws and set screws in your report.

Pilot hole diameters, as they compare to screw diameters, can play a critical role in the behavior of a device during testing and should therefore be included in your test report, as well. Pilot hole diameters may be particularly important for tests like foam block pullout testing. For pedicle screw testing, per ASTM F1717 and F2706, it is important to describe the distance left between the screw tulip and the test block to allow for potential failure of the polyaxial mechanism during testing. For interbody fusion devices with integrated fixation features, it is important to describe how the screws are fixed to the test blocks.

For your description of the test apparatus, be sure to provide important dimensions, and don't be afraid to be redundant with what is required by a test standard. For example, we recommend you list critical dimensions such as active lengths and moment arms used in relevant tests, as well as dimensions, such as the occipital cervical angle for ASTM F2706 testing or the intradiscal height for ASTM F2077 testing.

For test blocks, please state the test block material. For tests such as subsidence testing or screw pullout testing that utilize polyurethane foam to simulate the properties of bone, it is important to select the same grade of foam that was used to test a predicate if results are to be comparable. Test block dimensions should also be described and are, again, particularly important for polyurethane foam where sufficient distance between the tested device and the fixturing are necessary to prevent edge effects on the test results.

ASTM F2077 states that an engineering drawing of the test block should be provided, as the test blocks often have complex pocket geometries machined in to match the

geometry of an interbody device. The test block pocket depth should specifically be reported here, as well.

The degrees of freedom allowed or restricted by the setup and test machine are very important and can have large effects on the results of a test. Therefore, the degrees of freedom and hardware used to allow or restrict them should be well described. This can include hardware such as universal joints that allow bending, or a passive X-Y table that allows translation. There are also standard-specific fixtures that should be described as being in compliance with the standard, such as the fixtures in ASTM F2077 utilized for compression or torsion testing.

In addition to the physical hardware, the test machine settings that impact degrees of freedom should be described. For example, you should describe if angular displacement of the test machine actuator about the Z-axis is locked or free floating during a compression test. You should thoroughly consult the test standards, as many of these settings are defined as part of the standard methods.

The test environment should be described. It is often acceptable to test in ambient laboratory conditions and certainly more straightforward to do so. However, it is recommended that you test in solution of body temperature if the device materials are at all sensitive to temperature changes in this range, although many device materials such as titanium alloy are not affected by the difference between room and body temperature and can therefore be tested in ambient conditions.

Test solution is also recommended if you think analysis for any debris generated during fatigue testing may be desired. ASTM F1877 contains methods for characterizing wear particles. Wear standards, such as those for total disc replacements, have more specific recommendations regarding testing medium. However, spinal devices that are consistently subjected to wear evaluations are not within the scope of our discussion today.

Test setup images should be provided to include all relevant elements such as universal joints, push rods, and standard-specific fixturing. Some of the overall test setups may be large compared to the size of the device. In these cases, please also provide a close-up picture of the device in the fixturing.

Now we'll discuss some items to describe related to the testing procedure. State if any preloads are applied, such as an axial preload during a torsion test. Please also state how the preloads are maintained throughout testing. This includes situations where an axial load of zero is maintained on a construct, such as prescribed in ASTM F1717, during torsion testing of pedicle screw constructs.

Also describe the conditions that signal the end of the test, such as an abrupt change in displacement or loading or for maximum displacement or load-defined standard test. Specifically, for static tests, state the displacement rate or angular displacement rate used to conduct testing. For static torsion tests, state the direction in which torsion is applied.

For fatigue tests, please state the test frequency. We understand the higher frequencies can be desirable to complete a test faster. However, for high testing frequencies significantly above those of physiologic activities, you should consider the impact of the frequency on the material or response. For example, a viscoelastic material may not have time to fully deform or recover under a high frequency, which can potentially inflate the fatigue resistance of the device. And, of course, the test machine capabilities have to be considered for higher frequencies, particularly for tests that involve larger displacements. Please consult the test standards for any test-specific frequency limits.

Please report the R value, which is the ratio of the highest load to the lowest load applied during each cycle of fatigue testing. R values are usually prescribed in standard test methods.

Earlier in the presentation, the importance of fatigue precision was discussed. These

precisions are defined in many test standards for spinal devices, and this information can inform the load steps you take during fatigue testing. For example, if the fatigue precision required by the test standard is 1.25, your step-ups in loading could be 25 percent higher than the previous load to ensure adequate precision is achieved.

Deviations from standard test methods should not only be reported, but also justified. You should explain the impact a deviation may have on test results. For example, if you determine that it was necessary to epoxy an interbody fusion device to test blocks to apply torsion loads, you might state, "Use of epoxy to attach IBFD to test blocks is necessary to properly apply torsion. This may inflate the measured yield torque and stiffness as compared to testing without epoxy." In cases such as this, we would rather you test the device using such a deviation than not test at all; however, the impact of the deviation on the testing should be acknowledged.

In general, it is important to understand and acknowledge that many testing deviations may invalidate comparisons to the acceptance criteria listed in the literature or guidance documents, particularly those deviations that may inflate test results. Side-by-side testing of a device using the same testing deviations may be necessary for adequate comparison of mechanical properties.

For static tests, we recommend you present your numerical test results in a table such as the one shown on this slide. Results for each individual test specimen should be provided, as well as mean and standard deviation for each test parameter. For static tests, at a minimum, this typically includes stiffness, yield displacement, yield load, ultimate displacement, and ultimate load.

For fatigue tests, the results table should include specimen ID, the maximum and minimum load applied during each test cycle, the number of cycles achieved, and a description of the failure mode for all non-runouts. Consider also presenting results of

fatigue test data on a semi-load versus number of cycles plot with regression analysis.

A load displacement plot should be provided individually for each static test specimen. Each plot should include a stiffness line, the offset line which was used to calculate the yield value, and a marking for the ultimate load reported. In addition to the individual plots, test reports sometimes also include a single plot with all the specimens overlaid on one another. This can be a helpful way to depict how repeatable the test was.

Not all load displacement plots in the real world are as pretty as the one on the previous slide. It is important that you justify any irregularities in the curve that occur prior to the calculated yield or stiffness values. In these situations, it is important to explain what is physically occurring that is causing the irregularity. For example, for the plot on the left, the discontinuity could be caused by slight slippage of a device in a test fixture and not be representative of actual device failure. However, if the discontinuity is caused by a ratcheting mechanism in the device, slipping a tooth, this point is likely representative of device yield and should be calculated as such. In the plot on the right, the load stiffness region to start the plot may be representative of fixture settling. However, if it is representative of an initial device stiffness, this initial stiffness will need to be reported in the test results and potentially used for comparison to a predicate device.

The failure mode or modes for each test specimen should be reported. It is important to note that a single device may have multiple failure modes, such as a pedicle screw construct that may plastically deform in one region and fracture in another. Post-test high-resolution images of each test specimen should be provided with magnified images of the failure mode locations.

ASTM F3292 may be a useful resource as it contains recommendations for inspecting spinal implants for failure after testing. Please also include post-test pictures of test blocks if the blocks are significantly involved in the failure mode of the test. For example, if an

interbody fusion device with a coating is tested and a significant amount of coating is deposited in the test blocks during testing, post-test images of these test blocks should be provided. In addition to images of failed devices, high-resolution images of fatigue runouts should also be provided.

Now I'm going to pivot to just a couple of miscellaneous topics related to testing that we thought were important to bring up. In addition to putting together a thorough organized initial submission, thorough responses to additional information requests are also very important. Deficiencies related to testing are often at the top of the list in an additional information request. In order to facilitate a timely review of your responses, please list each deficiency in the additional correspondence verbatim. Then provide a narrative response to each deficiency or subpart that addresses all requested information in the deficiency. Describe any testing performed to address the deficiency and include comparisons to any acceptance criteria similar to how you would in an original 510(k) submission. If literature is utilized as part of your response, summarize the literature and provide copies. Sometimes we see instances where the response to a deficiency is simply "see test report." This is much less helpful as it is important for the narrative responses to put any testing performed to address deficiency into context.

Although this talk was focused on mechanical testing, cadaver testing can be a useful tool to evaluate questions related to bone-implant interface, device function, and the ability to implant the device in a repeatable manner. However, no standardized test methods exist for cadaver evaluation of spinal devices. Therefore, we recommend that if you intend to conduct cadaver testing to support a 510(k) submission, you submit a Q-Submission to discuss methods with FDA prior to initiation of your study, as we know these studies can be costly and time consuming.

Because review of the adequacy of the 510(k) summary is often the last thing we do

as part of our 510(k) review, it seems an appropriate way to end this talk. In your 510(k) summary, in the performance testing section, please list the specific tests performed on the subject device and reference any standards utilized.

Additionally, provide your overall conclusions for how the test results demonstrate substantially equivalent mechanical performance. For example, you might say, "The following tests were conducted in the worst-case subject device: static and dynamic axial compression, and static and dynamic torsion testing per ASTM F2077, and subsidence testing per ASTM F2267. Results of the tests demonstrate substantially equivalent mechanical performance as compared to a legally marketed predicate device."

This concludes our presentation. Thank you for listening, and we are available to take any questions you may have.

MS. STAROWICZ: Thank you so much, Kate and Jonathan, for presenting this very comprehensive information on spinal device testing. I think we can all agree there are so many different facets of testing to consider, and it's certainly important for manufacturers to understand FDA's expectations and critical success factors.

Equally important is having an understanding of sterility, reprocessing, and packaging considerations, and today, we are pleased to be joined by an FDA expert in this area, Steven Turtil. Steven obtained his master's degree in biology from George Washington University and has been a microbiology reviewer within the Office of Orthopedic Devices for 10 years, and he has been with CDRH for 20 years. He reviews industrial sterilization, packaging integrity and shelf-life testing and medical device reprocessing. He's an active contributor to both national and international standards development organizations.

So, Steven, over to you. We're all ears.

MR. TURTIL: Good afternoon and welcome. My name is Steven Turtil. I have been a

microbiology reviewer for 10 years within the Extracolumnar Spinal Devices Team of the Division of Spinal Devices within OHT6: Office of Orthopedic Devices.

I'll be going over the sterility content of 510(k) submissions, and at the same time I'll be citing submission weaknesses that reviewers most commonly identify, and that should help facilitate a more efficient review process for both reviewers and you.

This is an additional supportive title slide. It includes the full names of the two guidance documents that I'll be talking about. In addition, it includes the more casually referred-to names, FDA's sterile devices guidance and FDA's reprocessing guidance. Presumably, if you've had an opportunity to look at these already, you're probably familiar with the fact that they are fairly well written in a nice methodical manner and tell a really good story. I just wanted to mention that because one of the more common deficiencies that we come up with is we're having trouble understanding how your submission is put together. Please include an executive summary, tell us a nice methodical, logical story tying all the parts together.

This is a generalized overview of a typical 510(k) submission. Such submissions typically include sterile devices that are intended to be subjected to industrial sterilization processes. The relevant guidance document is FDA's 2016 sterile devices guidance. On the right-hand side you can see reusable instruments. These are also typically part of 510(k) submissions, and these are intended to be reprocessed by end users. The relevant guidance document is FDA's 2015 reprocessing guidance.

What we're going to be talking about first is circled on the left, FDA's sterile devices guidance. This is the sterile devices guidance table of contents. We'll touch briefly on the scope, definitions of the sterilization method categories, and then we're going to spend time going over the information to be included in submissions, the five items at the bottom of the slide.

The scope of this guidance is limited to devices labeled as sterile, that are subjected to industrial terminal sterilization processes, and by definition, based on ISO documents, these are devices that are sterilized within their sterile barrier systems.

Section IV defines the three different methods of sterilization: Established Category A, Established Category B, and Novel methods.

Established Category A methods are those that have a long history of safe and effective use as demonstrated by ample literature, clearances of 510(k)s, approval of PMAs, satisfactory quality systems inspections, and for which there are FDA-recognized consensus standards. Examples include dry heat; ethylene oxide in a fixed rigid chamber, not in flexible bag systems; moist heat or steam; and radiation.

Established Category B methods are those methods for which there are no FDA-recognized consensus standards. There typically is published information on these methods, and FDA has previously evaluated the validation data for specific sterilizers using specific discrete cycle parameters and determined them to be adequate. Examples include hydrogen peroxide, ozone, and flexible bag systems.

Novel sterilization methods are those that are newly developed, have little or no published information, no history of comprehensive FDA evaluation of validation data, and for which there are no FDA-recognized consensus standards. Examples include vaporized peracetic acid, high intensity light or pulse light, microwave radiation, sound waves, ultraviolet light.

Now we'll move on to Section V and look at the five items that reviewers typically have to document in 510(k) submissions.

This presents the first of the five items. Highlighted are the three points that have been asked for since 1990:

a. The sterilization method (for example, gamma radiation or ethylene oxide);

e. The dose for radiation (for example, 25 kGy or it might be a range, it may be 25 to 40 kGy); and

f. For chemical sterilants, the maximum residual levels and a justification.

In this version, highlighted in blue are items (b) through (d). These are the particular questions that help us identify when you may be presenting an Established B or a Novel method. And Items 2 through 5, we'll go through each of these individually, but in summary, they are the validation method and relevant standards, the sterility assurance level, any pyrogenicity claim, and a packaging description.

Let's take a closer look at Item Number 2, validation methods and consensus standards. For ethylene oxide and steam, we took -- we see overkill method of the half-cycle method mentioned, or a submission may mention both since the half-cycle method is a type of overkill method. For radiation, any one of these methods is acceptable. We most commonly see the VD_{max} 25 method. A distant second is Method 1. For consensus standards, these are presented in a table. I'm sure you recognize those. For moist heat or steam, ethylene oxide, radiation, dry heat, and for almost any other method, we're looking at 14937, general requirements for the characterization of a sterilization agent. There is a searchable database of FDA-recognized consensus standards, and the link is provided at the bottom.

Item Number 3, the sterility assurance level. FDA recommends an SAL of 10^{-6} for all devices labeled sterile. An exception is 10^{-3} for some devices that contact only intact skin. What is the sterility assurance level? By definition, it's a statement of probability. It's a statement of probability of a single viable microorganism occurring on an item after sterilization. And an SAL of 10^{-6} means that there is less than or equal to one chance in a million that a single viable microorganism is present on a sterilized item. Another way to say it, a more common way of saying it, is the probability that there is no more than one

non-sterile unit in a million.

Item Number 4. And here I'm introducing some red text. From this point on, red text is going to indicate an area where we commonly see problems and either omissions or indication of a deficiency in a submission. So, for a pyrogenicity claim, we're typically looking for a description of the method used to make the determination; a statement about testing frequency; an identification of the chosen testing limit; finally, an explanation supporting the selected endotoxin limit. This slide addresses the two items highlighted at the bottom of the previous slide, the identification of the chosen test limit and an explanation supporting the selected test limit. That is 20 EU per device based on the USP protocol for your typical device. For those contacting cerebrospinal fluid, 2.15 EU per device is acceptable, but there are very few orthopedic devices that I know of that contact cerebrospinal fluid. Also scattered here parenthetically are references to FDA's 2012 Pyrogen and Endotoxins Testing: Question and Answers, and also a breakdown of some of the acceptable metrics based on a 40 mL extract solution.

And Item Number 5, a description of the packaging designed to maintain the device's sterility and a summary of the package test methods. A simple summary would be sufficient. For performance, we're looking for simulated distribution followed by package integrity testing. And for stability, we're looking for aging, either real time or accelerated, followed by seal strength testing. Or a statement of conformity to ISO 11607 would be adequate. A more compressive submission might look like this; it would simply include all of the simulations and all of the test types as well as the standards used for each.

That takes us through the five items in the sterile devices guidance. Now I would like to share with you a few frequently asked questions.

Question 1: Are promissory notes acceptable? The answer there is no. We don't want to hear that you're going to be finishing your validations, we want to know that

they've all been finished.

Question 2: Is declaring conformance with 10993-7 adequate for ethylene oxide residuals? There also the answer is no. We want to know the maximum levels that you've met. That's what should be stated. And besides that, there are other sterilants other than ethylene oxide.

Question 3: For non-pyrogenic claims, do we accept LAL testing only, or do we accept the rabbit test? We accept any validated bacterial endotoxins tests. The rabbit test is considered a test for materials compatibility, so that doesn't really apply. That applies for materials compatibility, and there's a separate guidance document for that.

Question 4: Is non-pyrogenic acceptable instead of pyrogen free? And this is spelled out in the guidance document, and we prefer non-pyrogenic. Pyrogen free is really hard to establish.

And Question Number 5: Is product adoption acceptable, that is, into an already established worst-case family of products with an associated validation process? This might apply to sterilization or an aeration process. Some of the standards allow for that, so the answer is yes. Ethylene oxide, there's TIR28, and for radiation there's 11137-2, Section 4.2 and also TIR35. So this is a commonly-used approach, and we're okay with that as long as there is a standard that supports it, that FDA recognizes.

Now that we've finished talking about the sterile devices guidance, let's take a look at the generalized overview of a 510(k) submission again, and we can see on the right-hand side reusable instruments are typically included. These are processed by the end user. And the relevant guidance document here is FDA's reprocessing guidance from 2015. Also listed on the bottom are some of the standards that are typically involved. On the left-hand side, those are for industrial sterilization. On the right-hand side, TIR12 and TIR30, which we are looking forward to becoming a standard sometime in the near future, and the designation

number for that is ST98.

The scope of the reprocessing guidance document includes all medical devices requiring processing or reprocessing. That includes all reusable medical devices initially supplied as sterile, perhaps supplied as non-sterile, or that might be only be used by a single patient. It also includes single-use devices that are supplied as non-sterile but require processing prior to use.

The reprocessing guidance provides six criteria for reprocessing instructions. These include:

1. The labeling should reflect the intended use of the device;
2. Should advise users to thoroughly clean the device;
3. Should indicate the appropriate microbicidal process;
4. The recommendation should be technically feasible and include only devices and accessories that are legally marketed; and
5. The instructions should be comprehensive; and
6. Understandable.

We're going to skip over Number 1 because it's relatively intuitive at this point, and we all know which devices we're talking about.

Criterion 2 states that all reprocessing instructions should advise users to thoroughly clean the device. Several factors determine effectiveness of cleaning, and amongst these are energies, thermal energy, chemical energy, and mechanical energy. Each should be optimized for the cleaning challenge and material compatibility, and all specifications should be provided in the labeling.

So, two things here are clearly highlighted in red. The expression "thoroughly clean" is great when we see that, it's great when we see that. If you've got something close to it, that can be good enough. When it comes to specifications, really, really important, we

want to see all the details based on your validation activities. We can't stress enough the importance of including specifications. The caption reads, "That's not exactly what I meant when I said, 'please rinse.'" You have to give details in specifications.

Criterion 3 states: The instructions should indicate the appropriate microbicidal process for the device. As a quick introduction to the Spaulding classification system, there are critical devices, semi-critical devices, and non-critical devices. We're only going to concern ourselves with the critical devices. These are introduced directly into the bloodstream or are contacting normally sterile tissue or body spaces during use. Examples include all surgical instruments. FDA recommends thorough cleaning and sterilization after each use.

Criterion 4 states: Reprocessing instructions should be technically feasible and include only devices and accessories that are legally marketed. Ranges should not be used. It implies that all intermediate values have been validated and that FDA-cleared accessories exist for intermediate cycles, so we discourage the use of ranges. Part of the reason for that is there was a study back about 10 years ago trying to identify the cause for failures in healthcare settings, and they found out that about 80 percent of sterility failures are due to human error. So, what we want to do is limit, as much as possible, any chance that something may be misinterpreted.

Drying time is also highlighted here, not because of the reasons mentioned above, but because drying times are often omitted, so it's important to include validated drying times in your steam sterilization instructions. They can be non-standard, just not a range. And when I use the expression "non-standard," I mean it isn't consistent with the values given in Appendix C of the reprocessing guidance document. The details are provided here.

That reference to Appendix C is important because it introduces the concept of extended cycles, and extended cycles describe any sterilization cycle that includes

specifications that deviate from those found on commonly-used FDA sterilizers and for which there are limited or no FDA-cleared sterilization accessories. Again, please refer to Appendix C as indicated on the previous slide. Examples include cycles with longer exposure times or higher or intermediate temperatures. And directly from the guidance document, it states, "Implementation of extended cycles poses serious technical challenges in healthcare facilities." So, we're typically looking for something that is consistent with the values in those tables.

Most often -- and this is the note at the bottom, most often devices that can be sterilized using extended cycles can be sterilized using conventional Appendix C cycles. Not always, but most of the time, we get a lot of submissions that come in that have been cleared other places and the cycles are different and we consider those extended. And when we challenge this, 90 percent of the time, I would say, these devices can be sterilized in conventional cycles. For instances where a device is too complicated or too large to be adequately sterilized in the conventional cycles in Appendix C, we recommend that this disclaimer be included in the labeling.

Criterion Number 5: Reprocessing instructions should be comprehensive. We're going to go over most of these, but not all of them, primarily focusing on the ones that can be problematic in a submission.

Reprocessing instructions should include reference to special accessories. Most often problematic are references to trays and sterilization wraps, meaning, in particular, very little information is provided on trays and sometimes there is no mention of using an FDA-cleared sterilization wrap. This is an example of the type of deficiency you might see if you've omitted specification for a sterilization wrap. Your proposed labeling does not identify the sterile barrier packaging intended to maintain sterility of your devices. Please revise your device labeling to specifically recommend the use of an FDA-cleared pouch,

sterilization wrap, whatever you're recommending.

This is the type of deficiency you might see if you don't provide adequate information on trays. That's basically laid out in a manner that helps us determine whether these are general-use trays or whether they are dedicated to your particular device. That's the first part of it. And then later on we're looking for basic information on the trays, what they're made of, what their dimensions are, and also, we want to know that the labeling is adequate. Examples are given at the bottom there, do not stack trays during sterilization, of course, unless you validated them stacked, and that thorough cleaning should be included.

Criterion 5B: Point-of-use processing, instructions for prompt initial cleaning steps and/or measures to prevent drying of soil prior to cleaning to facilitate subsequent cleaning steps. Sometimes this is just not included, so we want to make sure that these devices don't have contaminants dried on them for a long period of time.

Criterion 5C: Disassembly and reassembly. Believe it or not, sometimes instructions are included for disassembly but not for reassembly. We need to know all the details. We look for step-by-step instructions with diagrams and photographs or illustrations wherever possible. We want to have left as little a chance as possible for doing this the wrong way. So, we don't like to see expressions like "disassemble if applicable" because it leaves the applicability to the discretion of the end user as to whether it really has to be disassembled or not.

Sometimes the end user can't tell whether they are disassembling it enough or too much. If they don't disassemble it enough, they're not going to be able to get the same results that you got during your validation for cleaning. If they disassemble it too much, they may be picking up springs and ball bearings off the floor for the next two weeks. So getting this just right is really important. It's kind of a Goldilocks moment; we want them to

be able to disassemble not too much, not too little, just right.

Criterion 5D: Method of cleaning. You may include a method for manual cleaning or for automated cleaning or a combination of both. Whichever you include, it should be validated. Specifications, again, are really important. So, we want to see all the details for every step: rinsing, drying, cleaning, everything.

Criterion 5E: Cleaning agents. Recommendations for use of detergents, enzymatic cleaners, and automated cleaning cycles should be consistent with directions for the use of the products. Highlighted at the bottom in red, mix according to the detergent manufacturer's instructions. Often there is nothing provided at all. The highlighted line is the one we see most.

Criterion 5F. This calls out the issue of final rinse water quality, and from the graphic nature of this slide, you probably already picked up that we've had some big problems with this. Item 5 in the middle of the slide there is verbatim from somebody's proposed cleaning instructions: "Remove the device and rinse for 2 minutes using warm-running tap water." Tap water is a big offense. Specific water qualities are recommended for this. Whatever this water quality is, it's the very last thing that's going to come in contact with the entire device before it goes to sterilization, so the water quality has to be top quality there.

More on that in a minute, but please note at the bottom, tap water is acceptable as an intermediate cleaning rinse for devices that are to be sterilized, and as a final rinse for devices that are about to go for high-level disinfection. And there's a follow-up slide to the previous slide on final rinse water quality. Please refer to AAMI TIR34, water for the reprocessing of medical devices. And you may also want to reference FDA's 2012 Pyrogen and Endotoxins Testing: Questions and Answers. The link is provided.

Criterion 5H: Visual inspection. All cleaning instructions should include a visual inspection. There are two reasons for this. First, for cleanliness. If a device does not pass

this test -- remember, visual inspection is a test -- then there should be steps identified that need to be repeated in the instructions. There should also be instruction for safe disposal of the device. Second, for functionality. The end user needs to have information to help them determine when a device has reached the end of its use life, and a description of unacceptable deterioration, such as pitting or corrosion, will help them make that determination.

Criterion 5I: Method of disinfection or sterilization. The top part of the slide talks about steam and ethylene oxide, and we'll come back to that in a second. The bottom part of the slide talks about newer proprietary methods, such as hydrogen peroxide and ozone. These methods have unique characteristics which vary from sterilizer to sterilizer and from manufacturer to manufacturer. So, if you're going to recommend one of these methods, it's important for you to include in your labeling the identification of the manufacturer of the sterilizer, identification of the sterilizer model, and identification of the specific cycle.

Back to the top part of this slide. Steam sterilization and ethylene oxide are sufficiently well standardized among sterilizer manufacturers such that sterilization cycles may be identified by the critical cycle parameters themselves. Please refer to Appendix C for the details on that. And speaking of Appendix C, this is a screenshot of that appendix. It's only one page that includes two tables, both having to do with steam sterilization. The top one has to do with gravity displacement methods. These are commonly referred to as gravity. And the bottom table, Table 2, refers to dynamic air removal methods, also known as pre-vacuum methods.

Highlighted on the right-hand side are two rows from each, at the bottom of each table, and it's indicated that they have no drying time or extremely short drying time. These cycles used to be known as flash steam sterilization cycles. That nomenclature changed about 9 years ago; they are now known as immediate-use steam sterilization

cycles, IUSS. If you choose to include immediate-use steam sterilization cycles in your labeling, it's important to note that they be designated as only for emergency situations. And if you want to include them, it's important that they be properly validated, that they be included in addition to routine sterilization cycles such as the conventional ones listed in Appendix C, and be clearly distinguishable from those other conventional cycles. It's important for them to be graphically separated. We like to see them in separate tables.

Finally, text should be included that clearly describes the circumstances for which they may be used. Intraoperative contamination is one of the common phrases that we like to see, for example, if something is dropped, if something is contaminated and it's needed immediately during the procedure.

Also occasionally omitted from instructions are specifications for drying times. This is a draft deficiency for such occasions. It states that "We are concerned that moisture remaining on the product after sterilization may result in the ingress of, and contamination by, water-borne microbes." It's always important to include validated drying instructions.

Criterion 5M: Additional labeling recommendations. This can cover a vast array of different recommendations that might go with your particular device. One that we're particularly concerned with, which happens occasionally, is that products that are non-sterile are not clearly labeled as non-sterile, and we want to see that kind of labeling placed on there. This is to avoid any possibility that somebody may pick up a product, assume that it's sterile, and use it in a non-sterile condition.

Criterion 6: Reprocessing instructions should be understandable. This is relatively straightforward. Instructions should be clear, legible, and provided in sequential order; in other words, don't present the sterilization instructions prior to the cleaning instructions. It should be written in simple language and sufficiently detailed to explain all the procedures and, wherever possible, we encourage the use of charts and diagrams or photographs to

help clarify the procedures that are involved.

These types of problems occur most often when text is written in one language and translated into another language. These are a few examples. "Store in house with relative humidity less than 80 percent, free of corrosive gas and good ventilation." Probably not what was intended by the people who wrote the instructions. The second block is disinfections. "The product recommended for disinfecting is a Biocidal that can be used with the state in which we find ourselves following the instructions provided in the package." Difficult to understand. Lastly, this is just an example of the importance of placing a comma in the right location or not placing it. Read as it's stated there, "Let's eat, Mom." Or without the comma, it would read, "Let's eat Mom."

Section VIII of the guidance talks about validation of the cleaning process. We're not going to dwell on that very much at all. Most submissions don't really require inclusion of validation data. Some of them do, and we'll talk about those in a minute. But just to give you an idea of what this is all about, at the Agency, we're always looking at the worst-case scenario. What's the worst that could possibly happen? Those are the things that we worry about the most, so we want processes to be established in such a manner that they will adequately address cleaning, in this case, processing of the worst-case scenario. What's the worst that could possibly happen? And the caption reads, "That, my friend, is why they invented the salad bar sneeze guard." What's the worst that could possibly happen?

Although we don't typically see validation data submitted in 510(k)s, it's important that you validate all of your cleaning processes and have that data on file. This is a simple summary of overall design of a cleaning validation process. We're thinking about worst-case scenario for contamination followed by worst-case scenario for implementation of the cleaning instructions. In other words, what is the worst that could possibly happen to soil the device and have soil integrated into the device during actuation, and what's the

worst case, the least rigorous implementation of the cleaning instructions? So, if one of the instructions says clean ultrasound for five to ten minutes, then the validation protocols should actually say ultrasound for five minutes, even possibly less.

Several places in the guidance document stipulate that all validation should be completed prior to submission. What we didn't put in the guidance document is a request for you to include a statement that you've actually completed that. So, this is a draft deficiency that you might receive if you have not provided evidence that you've actually completed all your validations. Highlighted at the bottom, "please confirm that all cleaning, disinfection and sterilization methods have been validated."

So, when do you have to submit cleaning validation data? FDA has identified a subset of medical devices that pose a greater likelihood of microbial transmission and represent a high risk of infection if they are not adequately reprocessed. So, these are the devices for which you do have to submit cleaning validation protocols and cleaning validation test data.

Appendix E presents devices for which 510(k)s should contain validation data for reprocessing instructions. This is a two-page screenshot of Appendix E, and highlighted as an example are arthroscopes and arthroscopic accessories. This is Table 2 of Appendix E. Instead of identifying particular device types, this table identifies particular design features that may be problematic when it comes to validating cleaning instructions. Highlighted are shaft-within-lumen configurations. These are common amongst orthopedic devices, for example, spinal implanters.

This is an example of inadequate cleaning instructions. Highlighted in the red circles are references to established hospital cleaning methods. There are no established hospital cleaning methods. Every device is different; every set of instructions for it should be different, and they should be validated independently. Also highlighted by the red

underline is the sentence: "Cleaning can include the use of neutral cleaners followed by a deionized water rinse." This provides an option to the end user. That does not help the end user; they need to know what they must do. If they don't include this step, does that mean that their instrument's still going be clean? It's unclear, so this is poorly written.

This is another example of inadequate reprocessing instructions. On the left-hand side, you can see the expressions "When necessary, clean," and "When necessary, disinfect." However, no guidance is provided to the end user as to how to make the determination of whether it's necessary or not, so it leaves it solely to the determination of the end user. Also indicated on this slide is the underlined text, use of "a general disinfection solution approved" for disinfection. Well, the FDA does not approve general disinfection solutions for disinfection, only high-level disinfection solutions. So, this doesn't have any meaning for the end user.

As a final example of inadequate reprocessing instructions, presented on this slide are two steam sterilization cycles. What you might notice first on the left-hand side is a listing of the preconditioning pulses. This is going to be meaningless to the end user and probably wind up only confusing them a little bit. We recommend that you never include preconditioning pulses in your labeling. Also listed here is a range for the temperature, 270 to 275. Again, we're looking for discrete specifications to go in the labeling. Also listed are exposure times of 10 minutes. For pre-vacuum cycles, there's no conventional cycle for a 10-minute exposure, so this would constitute an extended cycle. Notice anything else? Of course, there's no validated drying time presented in these instructions.

This concludes my presentation. Thank you for listening, and we're available to take any questions you may have.

MS. STAROWICZ: Thank you so much, Steven. You really covered a lot of ground in your presentation.

And to that end, I just wanted to let you all know that we've been getting a lot of questions that have come in throughout the day asking whether the webcast and all the slides presented today would be available, and the good news is yes, they absolutely will. They will be posted on the announcements page, the FDA website, shortly after the conclusion of today's workshop, and they will be up there for a period of one year from today. So, there should be plenty of time to go back, review, access all the great information presented today, and share that with your colleagues.

So, at this point, we're going to take a 15-minute break, and then when we come back, we're going to next dive into the topic of biocompatibility and you're not going to want to miss this one. So, see you back in 15 minutes. Thank you.

(Off the record 1:37 p.m.)

(On the record at 1:53 p.m.)

MS. STAROWICZ: Welcome back, everybody. It's now my great pleasure to introduce two FDA speakers who will share how manufacturers should be thinking about biocompatibility considerations for their devices, which is, of course, a very critical component of the premarket submission.

Our first speaker today is Anne Talley. Anne obtained her Doctor of Philosophy degree in chemical engineering from Vanderbilt University in 2016, and she has been with the FDA for three years and provides biocompatibility consulting reviews in the Office of Orthopedic Devices.

Anne will then be followed by Aprajita Garg. Apra obtained her Doctor of Philosophy degree from the University of Maryland, College Park, in 2012 and conducted postdoctoral research at Yale University School of Medicine. She has been at the FDA for four years and provides biocompatibility and sterility consulting reviews, also in the Office of Orthopedic Devices.

So, Anne, go ahead and take it away.

DR. TALLEY: Hi, good afternoon. My name is Anne Talley, and I am a reviewer in the Extracolumnar Spinal Devices Team of the Division of Spinal Devices within OHT6: Office of Orthopedic Devices. I will be presenting today, along with Dr. Apra Garg, on biocompatibility of orthopedic devices.

Here is the outline for our presentation today. We will go through the recommended endpoints for biocompatibility evaluation per FDA's biocompatibility guidance document and give an overview of several approaches to addressing biocompatibility of orthopedic medical devices with examples for each. We will finish up our talk by giving biocompatibility considerations for complex devices.

As I'm sure most of you all are aware of by now, CDRH's biocompatibility guidance document was finalized in 2016. The guidance document identifies the recommended endpoints for biological evaluation, which are based on the expected contact type and contact duration for the medical device. Most orthopedic devices fall into the category of tissue- or bone-contacting devices with either limited duration, which generally applies to instruments, or long-term duration, which generally applies to permanent implants.

You can see the list of the recommended endpoints on this slide, which is taken directly from Attachment A of the guidance document. In this talk, when we refer to recommended endpoints or relevant endpoints for devices, please keep this table in mind.

Now, before we start going over specific biocompatibility approaches, I'd like to point out the administrative requirements for addressing biocompatibility which are considered as a part of the refuse-to-accept, which is also called the RTA review of a 510(k) submission.

Specifically, the traditional RTA checklist recommends that each relevant biocompatibility endpoint, per FDA's biocompatibility guidance document, be addressed in

the submission. Additionally, for any testing that is performed, the RTA checklist recommends that you provide a full test report, which should include a description of the test article and any differences between the test article and the final finished device, the methods, your acceptance criteria, and analysis of results. In addition, for all provided test reports, we recommend that you provide a justification of how this testing supports substantial equivalence.

The ultimate approach to providing all of the identified information is to provide a rationale that biocompatibility testing is not needed, for example, when materials or manufacturing and processing are identical to the predicate. In the next few slides, we will get into examples of what this statement should include. It is also helpful if you provide an executive summary for biocompatibility either with your rationale that biocompatibility testing is not needed or a brief summary of all testing that has been conducted in support of your 510(k) submission. And this helps ensure that the information is up front and easily identified.

I would also like to point out that there are two draft guidances in orthopedics utilizing the safety and performance-based pathway, one for non-spinal metallic bone screws and washers, and the second for spinal plating systems. These draft guidance documents point to the CDRH biocompatibility guidance for recommendations for addressing biocompatibility in 510(k) submissions submitted through this pathway.

Next, we will get into the first potential approach for addressing biocompatibility, which is providing a risk assessment of the final finished device. This approach is based on the language recommended in Attachment F of FDA's biocompatibility guidance document. Here, the rationale can be applied when the subject device is identical to the predicate, and this applies both to implants with long-term contact as well as instruments with limited contact.

Example documentation language is copied here from Attachment F of the guidance document, comparing a final finished device to the legally marketed predicate. The legally marketed predicate can be your primary predicate or an alternate reference device. We recommend that, if you use this approach, you consider any differences between the subject and predicate device in terms of design, indications, type and duration of contact, and how these differences may impact biocompatibility.

There is a flowchart in Attachment D of the guidance document that provides additional details on comparison criteria. If you intend to use this approach in a 510(k), I want to highly stress that we recommend you provide this exact language. If you use terminology such as similar or equivalent, we will have additional questions about any potential differences.

In cases where there are differences between the subject and predicate device, it can be acceptable to use terms such as similar or equivalent. However, we recommend that you describe any differences in the manufacturing and processing steps, including all potential differences in manufacturing residuals, and address the biocompatibility risks associated with these differences.

In this example, there are differences between the subject device and the predicate device, but both devices are from the same manufacturer. If the differences relate to a change in manufacturing process, we recommend that you provide a side-by-side comparison of the manufacturing process and evaluate risks for each recommended endpoint from any new or increased manufacturing chemicals.

Another approach using the example language from Attachment F can be if the subject is identical in material, intended use, and manufacturing to a predicate device from a different manufacturer. This approach can be acceptable if the third-party contract manufacturer provides a letter stating that the subject device is identical to the predicate

device. In this case, the letter should include the predicate device trade name as well as the 510(k) number.

Now we will move on to Approach 2, which includes a risk assessment of the manufacturing process for the subject device. This approach can be applied to both implants with long-term contact as well as instruments with limited contact. In this case, it is helpful if you provide a manufacturing flowchart with sufficient details in the manufacturing process, including raw materials, manufacturing, processing, and methods and all manufacturing aids. This is important so that you provide a detailed description of all potential biological risks associated with the raw materials and manufacturing and processing for the subject device.

Along with a description of the raw materials and potential manufacturing and processing residuals, you can leverage any available biocompatibility information about the process and chemicals to address the recommended biocompatibility endpoints. This biocompatibility information could include literature or safety data sheets for the manufacturing chemicals. Please note that, in general, it is not appropriate to leverage clinical data to address biocompatibility endpoints, as clinical studies are not designed to collect sufficient data to address all of the recommended endpoints.

Example 3 describes a case where the submission is provided with adequate description of the manufacturing and processing and relevant chemicals, but the recommended endpoints are not adequately addressed. In the example on the right side of this slide, this is a case where a polishing step was described along with the relevant polishing media. However, no adequate justification is provided to address each recommended endpoint from the biocompatibility guidance document.

Example 4 describes a case where a submission is provided with a description of the manufacturing and processing steps, but the associated manufacturing materials are not

identified. We recommend that you identify all manufacturing materials associated with each of the manufacturing and processing steps, and assess the hazards associated with the relevant biocompatibility endpoints for each manufacturing material. Please note that justification based off of cleaning validation alone, including cleaning validations that are performed in accordance with ISO 19227, are insufficient if provided as a standalone justification for not conducting a biocompatibility assessment.

The limitations of this approach include that, unlike extractable and leachable studies, cleaning validations rarely include analysis of polar, mid-polar, and non-polar solvents, and the analysis techniques are generally limited. Extraction is generally not conducted under exhaustive extraction conditions as defined in ISO 10993, part 12, and the identified endpoints, which can include total organic carbon and total hydrocarbon, are difficult to interpret with respect to the relevant biocompatibility endpoints. And finally, the individual extractable and leachable compounds generally are not quantified and assessed. Therefore, we recommend that you provide a full biocompatibility assessment that addresses each recommended endpoint as discussed previously.

There could be circumstances, however, in which cleaning validation test reports could be requested for devices as a part of a biological risk assessment. These may include cases where implants or instruments have complex geometry, when devices are manufactured using additive manufacturing as opposed to subtractive manufacturing, or when cleaning aids are used following passivation or anodization.

Now I will turn it over to Dr. Garg to continue with the rest of the risk assessment approach examples.

DR. GARG: Hello, everyone. This is Apra, and I will go through the rest of the biocompatibility slides.

So, the Examples 3, 4, and 5, described earlier by Dr. Talley, provided critical inputs

to conduct biocompatibility assessments based on manufacturing process, that is, the entire manufacturing process and associated manufacturing materials should be assessed for hazards.

This slide includes example of a justification that can be utilized to limit assessment to certain manufacturing materials and processes, and the justification is based on presence of a manufacturing process that are known to lower risk from manufacturing materials. This justification is applicable to a metal-based device, and it can be utilized if the raw material, also called a material of construction, is in accordance with an FDA-recognized material standard and has history of use, and the manufacturing process includes passivation or electropolishing or anodization type II or type III. It's recommended that passivation and electropolishing is conducted in accordance to an FDA-recognized consensus standard such as ASTM F86. So, in this situation, you may limit assessment to process and materials downstream to passivation or similar risk dual-limiting process which are stated here.

This slide provides an approach for a risk assessment of a polymer-based device. In my opinion, polymer-based devices are generally more challenging for biocompatibility review compared to standard metal-based devices. And Example 7, that is included here, includes justification for a polymer-based device. So, for these kind of devices, the biocompatibility assessment for raw material may be supported by testing conducted by a vendor and submitted to the Agency in a master file along with manufacturing recommendations. Please be advised that material standards for polymers are typically not acceptable to support raw material biocompatibility.

And thereafter, if no manufacturing material is used during manufacturing, for example, on a machine done without the use of a cutting fluid, lubricant, cleansers other than water, for example, we have seen this case to be applicable to a PEEK-based device.

And so, in that case, biocompatibility risk from manufacturing process is mitigated, and therefore, raw material information alone may be adequate to support device biocompatibility.

Assessment of a manufacturing process that utilizes animal-derived material needs additional consideration. Animal-derived material-based devices are reviewed for additional risk, such as risk from pathogens that reside in animals. So, if an animal-derived material is used as a device component or during the device manufacturing process, please refer to the recent 2019 FDA guidance, Medical Devices Containing Materials Derived from Animal Sources, for information that needs to be submitted.

The Agency recommends assessment on a final finished device, so packaging and sterilization should also be assessed. Packaging material assessment becomes more relevant for materials with limited history of use, such as a nylon bag used as -- device package. Evaluation of sterilization process is also relevant, and in some cases, this evaluation is straightforward. For instance, interaction of a metal-based device with radiation or steam sterilization is well understood. However, for a polymer-based device, if polymer master file used steam-sterilized test article while a subject device is ethylene oxide or hydrogen peroxide sterilized, then in that case, you will need to assess the effect of the sterilization modality, either ethylene oxide or hydrogen peroxide, on raw material, manufacturing material, and device surface characteristics.

For absorbable devices such as polylactides, polyglycolide-based devices, additional risks should be considered. These materials are sensitive to manufacturing processes such as temperature, purging. Additionally, raw material shows wide variation in molecular weight, residual monomer content, crystallinity, et cetera. Hence, use of manufacturing-based approach alone to support biocompatibility is challenging.

Several of the orthopedic devices have coatings such as hydroxyapatite, cp-Ti, or

titanium/hydroxyapatite dual coating. The biocompatibility assessment for a coated device may include testing conducted by a coating vendor and the information available via a master file. Alternatively, if there is a marketed device with identical base material and coating, then prior clearance may be leveraged. But in this situation, it is important to compare the subject and the reference predicate in terms of indications, type, duration of contact, et cetera. Also, additional assessment on post-coating process is needed.

Our goal is to complete review in a timely and efficient manner, and therefore, we recommend that the reason for submitting test report is included. For example, you have a new device with no prior assessment, or there is a change in raw material or manufacturing process, and you chose to conduct testing to address relevant endpoints. So, in this case, it is recommended that you include the test report in a submission. However, if it is stated, the subject device is identical to predicate as described in the Attachment F of the guidance, and there are no device-related complaints or MDR that points towards a concern, in such cases, the relevance of testing is unclear, and a clear reason should be included.

Another approach to conduct biocompatibility assessment is using a combination of chemical characterization and biological testing. In this case, we are referring to use of analytical testing to conduct chemical characterization. The standards listed on this slide provides recommendation for analytical testing and toxicological risk assessment. ISO 10993 Part 18:2020 provides recommendation on analytical testing. It is a recent publication and has partial recognition by the FDA. ISO 10993 Part 17 provides recommendation on toxicological risk assessment. This standard is undergoing major revision. And ISO/TS 21726 is a relatively new standard and also provides recommendation on toxicological risk assessment.

Additionally, CDRH provided scientific perspective on this topic in a webinar, the

slides for which are available at this link. The Agency's 2016 biocompatibility guidance also provides recommendation on chemical characterization.

So overall, you can see there are standards and guidance available that provides recommendation for analytical testing. Still, due to either recent recognition or revisions, there appears to be a wide variation in analytical test methods across different test specificities, and therefore, often, in a submission, if there is analytical testing, additional information is requested to ensure the testing is conducted adequately so that the data can be relied upon as worst-case extractable or exposure from the device. Therefore, if you propose to or plan to conduct analytical testing, a Q-Sub is recommended for feedback on the test protocol.

Another consideration for analytical testing is, while it can be utilized to address endpoints, acute systemic toxicity, subacute/subchronic systemic toxicity, chronic toxicity, genotoxicity, carcinogenicity, it may not be adequate to address cytotoxicity, irritation, sensitization, material-mediated pyrogenicity, depending upon availability of chemical-specific data to address these endpoints.

Additionally, it also cannot address implantation endpoint, and testing may be needed depending on device type, such as if a device contains some unique surface properties or geometry. So due to this, this approach to conduct biocompatibility assessment was called a combination approach, so it will need both analytical testing and biological testing. You may also choose to conduct biocompatibility assessment based on only biological testing. The standard, ISO 10993 series and FDA biocompatibility guidance, provides recommendation on biological testing. Please note, if a failure is observed in any of the testing, a root cause analysis is requested. So for instance, if failure was noted for cytotoxicity testing, then a justification that irritation study test may not be adequate.

Additionally, if during this biological testing the device is extracted in different

extraction vehicles, the test report should provide information on extract and device after extraction. If color, cloudiness, particles are observed in extract, or corrosion or discoloration is observed in the test article, a justification should be provided for why these were not a present clinical concern. This will likely be a collaborative work between the test house and the sponsor to understand what can be the possible cause. It may need additional testing, so for instance, if particles were observed, you may need to understand the chemical composition of particles to actually clarify where these particles are coming from.

The special 510(k) guidance was published in 2019. Test reports are generally not reviewed in a special 510(k). If biocompatibility testing is needed as part of risk mitigation for your subject device that you propose to submit in a special 510(k), please refer to Appendix C, Table 2 of the special 510(k) guidance as it provides example of sundry information for biological testing that could be included in the submission. So, in this way, we still get to review important aspects of testing without looking at the complete test report. Please be advised, analytical test review is not appropriate for a special 510(k).

In the last two slides, we will provide additional considerations for devices that we're putting in a bucket and, for the lack of a better term, calling them as complex devices. Devices such as absorbable devices and in situ polymerizing devices are in complex device category to remind that these devices need additional considerations. For example, an absorbable device may need evaluation of in vitro degradation, additional implantation endpoint, sample preparation justifications, et cetera. Devices with wear particle generation concern also needs additional studies as routine biocompatibility testing may not be able to address risk from wear particles, and a Q-Submission is recommended to discuss biocompatibility assessment approach for such devices. Antimicrobial devices are also in complex device category. Many of these are combination products requiring both

device and drug review.

Similarly, devices with nanoparticles or nanofeatures may present hazard and also interfere with biocompatibility assessment. And again, for such devices, a Q-Submission is recommended to discuss biocompatibility assessment approach.

This concludes my presentation. Thank you for listening, and we are available to take questions you may have.

MS. STAROWICZ: Great. Thank you so much, Anne and Apra, for your presentations.

And now, at this point in the agenda, it's time to hear again from our audience. There's more polling questions. And so, Brent, I will turn this back over to you.

DR. SHOWALTER: There we go. Thank you very much, Sharon.

So yes, we are very much looking forward to your feedback. And I'm pulling up the slides here. So for those of you who were here this morning, these Menti sessions are very similar to what we've done before, and for those of you who haven't joined us, two ways to participate. So the first is to go to Menti.com and there will be a code related to this, so the code for this particular session is 46-24-26. There's also a slide with a QR code, so you can scan that with your phone and that will take you directly to the survey.

So, with that, I believe we can go to the first question. We'll give people a few more minutes to log in and see that. So, we have a number of questions for you. Several of these questions are actually more freeform than we had this morning. So, if we can go to this question.

The first question is: How often do you use finite element modeling in determining the worst-case construct for performance testing? And the answers that you could potentially give are never, sometimes, frequently, and always.

So, a number of people have started answering this already, and about 50 percent uses sometimes, and then the next most common answer is frequently. So about a third of

participants are saying that they use finite element modeling frequently. The two ends are never, which is low, 2 percent right now. And always is around 10 percent. We'll give those who are joining a few more minutes to chime in.

But this was a topic that was discussed by Jon and Kate during the performance testing section this morning -- this afternoon, I should say, right after lunch. And so we're curious how often finite element modeling is used in your design process because we don't always see that in the submissions themselves.

So, it looks like the number of participants are slowing down, so we finalized with around 4 percent of participants saying that they have -- they rarely or never use finite element modeling, about 60 percent use it sometimes, 30 percent use it frequently, and 10 percent use it always. So thank you for that first question. If we could move on to the next slide.

The next question says: The Division has published articles and guidance documents describing mechanical testing results for interbody cages and plates. So, the question we want to ask is: Do you use this? There are five potential responses: never, sometimes, frequently, and always and then the last option is not aware of it.

So, with about 40 people responding so far, we have about 10 percent is never, 20 percent sometimes, and then frequently and always are around 35 percent each. This is good news for us; it means that it seems, at least from the participants who have responded so far, that our efforts to put out these guidance documents and these publications, it seems like they're being used frequently in your design processes and in your submissions.

And we'll give it a few more minutes for people to answer because more answers are coming in, although the percentages aren't changing that much from the initial responses. But keep this question in mind. We have some more freeform questions coming up. So, there will be some questions related to these types of articles and guidance documents, but

we need a little bit more feedback.

All right, it looks like the comments have stabilized a little bit, so again, around 35 percent of individuals have said that they frequently use these types of results, and another 35 percent say always. So, a combination of about 70 percent of individuals use this quite a bit. Thank you, everyone, for that feedback. We will move on to the next question.

This one: Should device-related information such as raw material and manufacturing material/processes be discussed with the biocompatibility test house?

So, we have 50 people responding already, and right now, everyone says a hundred percent, so I think that's a pretty clear answer so far. We'll keep that up for just a second longer. It seems pretty straightforward. All right, if we could go to the next slide.

So, this is fairly similar, so is a description of potential manufacturing residuals alone sufficient to support biocompatibility of a metallic implant?

And for this, as we've mentioned -- as Sharon mentioned earlier, slides for talks will be posted after this meeting ends, and so Apra's talk and Anne's talk had some great answers to this. They have separated out different conditions and some of the main things to look for in determining biocompatibility.

But as individuals have noted, we have about 50 people who have responded, and 85 percent said -- talking about the residuals alone, 85 percent say that's not enough, and 15 percent say that is enough. And as the majority of the group have indicated, the residuals, while it is a very important part of biocompatibility, it's not quite everything you need. There are a few more pieces of information that are useful, including a description of the raw material, a little bit of detail about the manufacturing processes themselves. So, with that, we will move on to the next question.

Okay, so I'm glad to see there are a lot of people who have responded to this already: So, in what spinal device product areas would you like to see additional guidance?

So, I'm going to read a number of these. These are things that we're going to be taking notes on and look for potential ways, things that people really want a lot of, to see if it's repeated issues. But some of the ones that have been mentioned are use of saline over bovine serum in testing. Nanofeatures and additive manufacturing. I will point out that the additive manufacturing group, I know, has been working quite diligently on a guidance document to put out.

Some other topics that people have mentioned include spinal device testing and acceptance criteria. So, with that, Jon and Kate have mentioned some of the guidance documents that have come out, and I think the goal is to keep going -- to keep adding different products to that. It is a little bit of a time-intensive and resource-intensive process on our part to compile that information and put it together. So, we're trying to hit the products that have the highest volume first, but we'll keep adding to that.

Some other things that have come up are use with allograft, SI devices, loaner, consignment kits. Is there any way to scroll down? Thank you. So, repeated to some of the things that we've seen so far, bioactive materials, safety and performance pathways, so there are several comments about performance standards. Additive manufacturing has come up a number of times, and that tracks with a lot of what we're seeing in our -- on our end, as well. So, I would say over -- as time progresses, we see more and more submissions that are for additive manufacturing, cages in particular, but other devices, as well. So that tracks with -- and it's good to know what industry is thinking, as well.

So, I'll read just a couple more, and then we'll go to the next question. So, some other topics that people have -- are interested in include motion preservation of the spine, including artificial discs, non-screw standalone cervical devices. Let's see. And yeah, there are several related to things like allograft, HCT/P tissues, bone graft substitutes, things of that nature. So that's good to hear that there's a lot of interest in that. So, thank you,

everyone, for giving us a number of things to look at, but we're going to move on to the next question, which again is a freeform response.

So, this says -- this question reads: Aside from mechanical testing, in what nonclinical testing areas would you like to see additional clarity, such as sterility, biocompatibility, and MR?

So just in a quick scan, it looks like half of the responses are biocompatibility and another third are about sterility. There are a few on animal studies, those are -- animal studies are definitely -- they're tricky, right, they're expensive and they take a lot of time for people that need to do them, so I can see why that would be a topic of interest. A number of questions on sterility. One of them is coming up as wear debris, and I think it's related to 3-D printing and additive manufacturing, and so that's going into the -- tying into the responses that we saw from the previous question. Related -- well, somewhat related to the animal testing, there's another recommendation to look at cadaver studies. This is something that Jon Peck mentioned briefly in his talk about some of the cases for that, but yes, we can see that there's a potential need for guidance in that area. With that, we will move on to the next question, please.

This one is somewhat similar, so it says: Do you see areas of performance testing that need additional standardization?

So, there are some answers of not sure and not applicable, a number of yes. So the ones that say yes specifically state subsidence, so subsidence testing. Another one is interbody devices that use anchors. As noted when the first guidance documents came out for spinal -- for interbody devices, they didn't have anchors and now several of them do, so it might be useful to add some performance testing for that. There's a comment about PCF foam for different applications and the type of PCF to choose for each test.

So, it looks like comments have stabilized for that question, thank you. Oh, we've

got a few more. So, a number are adding questions about things like SI screws and facet fixation. All right. And with that, I think we're ready to move on to what I believe is the last question.

This one is the same question that we've asked at the end of every Menti session. Do you have any feedback for the Division of Spinal Devices or OHT6 at large in our review of performance testing in 510(k) submissions?

So, we have a number that say no, but we have a couple things that we need to look at. One of them is for reviewers to look for answers before asking the sponsors, we'll take that under advisement. So we'll work on defining things. And I think a lot of the answers to this question could be summed up in the answers to the previous question. So, we're trying to identify areas for additional guidance documents or clarification. So, we're grateful for the comments that express things and appreciation, so -- and with that, I believe that we will wrap up.

So, thank you, everyone, for your participation. We genuinely appreciate the feedback, and if you have any longer comments that aren't appropriate to put up on a Menti survey like this, please continue to send them to our e-mail inbox. Thank you.

MS. STAROWICZ: Great. Thank you so much, Brent.

And on the agenda, this brings us actually to our third and final industry panel session for the day, and in our earlier panel session you may recall that I referred to the indications for use and the device description as the heart and soul of the submission. Well, in many ways, I feel that performance testing is actually the skin and bones, and pardon my pun in that, but certainly and especially in the area of orthopedic devices, it is -- takes a very prominent place.

So today I have the pleasure of being joined by three distinguished panelists who have extensive experience in this area, and I'd like to just take a moment to introduce them.

So, the first panelist is Lisa Ferrara. Lisa obtained her doctorate in biomedical engineering with a concentration in microelectromechanical systems. She has been the owner of OrthoKinetic Technologies, it's a medical device regulatory consulting firm, and OrthoKinetic Testing Technologies, which is A2LA accredited in IEC/ISO 17025, certified medical device test facility, and she has been the owner/operator for the past 11 years. She's authored numerous technical publications, book chapters; she's been granted multiple patents; and she presents -- frequently presents on novel technologies, including biomaterials, nanotechnology, musculoskeletal and spinal biomechanics, biomechanics of brain injury, additive manufacturing, and regulatory strategies.

So welcome, Lisa.

DR. FERRARA: Thank you. It's a pleasure.

MS. STAROWICZ: The next panelist is Danese Joiner-Fox. Danese is a senior staff regulatory affairs specialist within the trauma and extremities division of Stryker. She has six years of regulatory experience both combined at FDA as well as at Stryker, where she's been since 2018, and overall nine years of orthopedic research experience. Danese holds a master's degree in mechanical engineering and a Ph.D. in biomedical engineering from the University of Michigan, Ann Arbor, and she's conducted postdoctoral research at the Van Andel Research Institute in Grand Rapids, Michigan. She's the author of numerous peer-reviewed papers and conference abstracts. She serves on biocompatibility and additive manufacturing working groups, both within AdvaMed and also within the Orthopaedic Surgical Manufacturers Association, or OSMA.

So, Danese, welcome to the panel.

DR. JOINER-FOX: Thank you, Sharon.

MS. STAROWICZ: And last, but certainly not least, we have Dawn Lissy joining us. Dawn is a biomedical engineer and entrepreneur and an innovator since 1998, the Empirical

family of companies, which includes Empirical Testing Corporation, Consulting, and Empirical Machine, operated under Dawn's direction. Empirical offers a full range of regulatory and quality systems consulting, mechanical testing, prototype manufacturing, and validation services to bring the medical device to market.

So, I'm so pleased to have you all join me here today to cover a very important topic. I think what we'll do to maximize our time together, which will come and go very quickly, is we'll start off with a discussion focused more on the mechanical performance testing with Dawn and with Lisa, and then we'll then shift over and transition to Danese for a discussion on biocompatibility.

So, with that being said, just to kind of get us started, a question for you, Lisa. You know, we've heard several times today about projects such as project ORCA, which we know originated in the spine group, where existing mechanical testing data has been compiled and published by FDA. And this really serves as an option to provide acceptance criteria for manufacturers through more of a safety and performance-based pathway as opposed to the extensive time and costs that's traditionally associated with head-to-head testing against a predicate device. I'm just very curious. With your experience and your clients, are many clients utilizing this approach, and can you speak a bit to the direct benefits?

DR. FERRARA: Definitely. Many, many clients are using this approach. Most of mine would use this for the published data that's out there, and it's important from different aspects. One is it provides the criteria that has a margin of safety to it, which has been validated against human tissue, in vivo, physiological and biomechanical tolerances.

With that said, it allows the companies that are manufacturing and designing devices to design to that criteria, and then also, with the testing, we'll know that it will meet that criteria. It also minimizes added feasibility testing where they have to go back and perhaps

choose their design, modify it to strengthen it or perform in a different way to meet the criteria. So, it takes out that step. It also makes it a much more efficient submission showing that you've got equivalence to multiple devices that have performed within a specific range.

MS. STAROWICZ: Right, excellent. I know oftentimes those challenges with just, frankly, sourcing competitive products or a predicate product, too, to be able to conduct that testing. So, we definitely have heard great feedback in that area. I'm curious to know your experience, as well. Thank you.

DR. FERRARA: Thank you.

MS. STAROWICZ: Dawn, a question to you. In your opinion, what do you see are the most common areas for performance testing deficiencies? I know you work with a lot of well-published companies of all sizes, but especially smaller companies. What should companies really be mindful of as they approach mechanical testing of their devices?

MS. LISSY: Sharon, it's good to see you. Nice job today and thank you for asking me to be here.

First of all, I want to say kudos to the FDA for tackling one of the biggest challenges for anyone who wants to take a device to market. And that is, you know, we all know that there's 10 to 12 to 15 different things for substantial equivalence, but the mechanical testing is really what sort of leverages and gives people heartburn about is their device safe; is it going to pass substantial equivalence? And so the guidance documents for the plating system and the published articles have been a huge asset for this industry 30 years later after I started, so that's been the constant thing.

Even with that information, people still run into roadblocks on what should they be doing with their mechanical testing, and the number one thing is making sure that they pick the correct size to represent worst case for their entire battery of testing. And then the

second part of that is making sure that they justify that worst case. And Jonathan and Kate did a fantastic job earlier walking through what does the justification look like, what will we accept or what will the FDA accept.

Next is testing the correct number of devices in each mode. Sometimes I have clients that say, oh, well, I just want to do the two runouts. And I said, well, but they're also looking for how is the device failing and is it consistent with its failure mode, because that's a trigger for more conversation. Especially with additive manufactured devices, this is a bigger concern. Orientation of cages in shear mode is something that we get feedback on and taking into consideration the surgical orientation of the device and then testing it appropriately.

What is failure? This comes up when it's for, for instance, an artificial disc that may not actually experience a crack or a fracture. So, what is defined as physiologic failure and relevant mechanical testing failure? And then lastly, your test block design and the fit of the implant. These all together will impact the outcome of the mechanical testing.

MS. STAROWICZ: Great. No, excellent. I think Jonathan touched on a number of these, as well, earlier --

MS. LISSY: I'm only reinforcing what they said.

MS. STAROWICZ: Yeah, I know. That's wonderful.

And then, Lisa, we're fortunate in the spine to have a number of standards and testing standards and such, but how do you advise clients who -- you know, for approaching performance testing where there may be very few standards, regulations, or special controls for their particular device?

DR. FERRARA: This is a great question, and I love it because I spend most of my time in this realm, which is enjoyable. And again, I commend both Kate and Jonathan for their presentations and even touching upon the cadaver testing. A lot of that goes into

something like a cadaver test.

But where we go with this is, when there's nuances to 510(k)-able devices that are coming out there, new technologies that are within that pathway, but there isn't a set standard, so what we have to do is take a step back and really assess what that main objective is. What is the nuance or the difference? What is the objective of what you're trying to show? What are the risks? How would you mitigate those risks? What is, most importantly, the clinical relevance of it?

So, you take this information as a whole and start to build your protocol and your design of your test method based on that. The two avenues you can take, obviously -- or three -- is one, design it as a bench-top model, which is taking that clinical relevant route, trying to make sure you're applying loads and stresses, strains, et cetera, that are super physiological, that provide a significant margin of safety so that you know you're hitting your acceptance criteria but you've gone beyond that. In other words, you've taken it so that you really are testing a worst-case scenario as a whole.

With respect to what Dawn was saying, too, she's right with choosing the right sizes, et cetera, but it's also adding back that you've got to design your test that doesn't have a standard or known criteria to work in this situation so that you're outside of the Bell curve, you're into the tail of the curve or -- the curve and you can address that margin of safety as well, when you design that test.

It doesn't apply to strictly a bench-top test. That's when cadaver testing should come into play. I spent many years, many years with cadaver testing, and that's when you start to bring it in. And, again, cadaver testing is so specialized because it really is designed for specific objectives and for specific clinical relevancies, as well. That can be challenging, as you know, because of the variabilities that exist. So, it's nice to be able to design something where you can have both a bench-top model as well as incorporating, perhaps,

some cadaveric testing, as well.

MS. STAROWICZ: Great. Right, excellent.

Well, I just -- a little bit of 3-D printed devices. We've heard that also a few times mentioned in various presentations today, and certainly they're becoming much more prevalent. FDA has issued guidance in this area, but deciding what specific type of information to include in a submission and how do you go about defining those boundaries for a variable process, I'm assuming, can be very challenging. Are there best practices, Dawn, for doing this? And how does one kind of strike the right balance in determining the extent of that manufacturing information that normally would never be included in a 510(k) but, you know, what is the right amount of information that would be appropriate to include in the premarket submission?

MS. LISSY: You know, it's interesting, Sharon, because a few years ago I was at a conference where the owner of an additive manufacturing company said, I see that there will no longer be subtractive manufacturing in 10 years, and I was like, how about the mechanical properties of additive manufactured devices and the impact? And by the way, all the things that aerospace and all the other industries that use additive manufacturing don't care about, they don't care about clean or sterile or residual or anything that's left. But on top of that, they're looking for device -- their pieces to actually break in a systematic defined manner, and we're looking for our devices that last for longer than the 20 years that we designed them for.

So, there's a lot of information out there, but we need to look at what's relevant for a medical device. So, first of all, use the guidance documents. The FDA has done -- they have done a fantastic job of being relevant and current with what we know that's applicable as this technology emerges.

Make sure that all of your parameters are considered. Whether you're using virgin

material or recycled material or recycled powder, where is the printing location? How are you removing the powder? I've been to a number of conferences where people just sit and talk about the cleanliness of the device, and those are concerning things that we need to be systematically correct about, right, because we're concerned about long-term effects of that material in a human body. Making sure that you print for a worst case for all of your testing, so whether it's for a torsion test which might be a different height than an axial compression test.

And as far as the manufacturing aspect, besides those pieces that I've already talked about, you want to make sure that the manufacturer that you're working with has a validated process. I often have clients that say, well, they're FDA registered; fantastic. They're ISO 1345; also fantastic. Do they have a validated process? Is there reproducibility that's going to happen that, no matter what happens, you have confidence in the interval?

And the interesting thing about additive manufacturing is that small changes in a process can have big impacts on the output and the fatigue performance of the device. And so those are the things that, above and beyond a subtractive device, you want to make sure that you're addressing for simplicity and consistency.

MS. STAROWICZ: Great. Well said, well said.

I'd like to get Danese into the discussion now as well, too, and shift gears maybe a little bit more toward the biocompatibility side. So, Danese, from your experience both as a former FDA reviewer as well as on the industry side now, what do you think are the most common areas that you've encountered for biocompatibility performance testing deficiencies, and what should companies be mindful of as they approach the assessment of their devices?

DR. JOINER-FOX: Great. A great question. So, some of this was highlighted with the wonderful presentations we've seen from FDA, but in my experience, some common things

that come up are not addressing all the recommended endpoints that are outlined in the biocompatibility guidance document. In addition, sometimes companies will fail to address biocompatibility of the instruments. A lot of times focus is placed more on the implants, and it's sort of an afterthought to think about the instruments.

In addition, I've seen failure to provide full test reports and risk assessments that really focus only on the biocompatibility of the material and really aren't looking at all of the processing effects, the geometry, the sterilization, and you have to remember that biocompatibility encompasses all of these things. In addition, I've seen and run into failure to provide actual submission numbers, and when you're utilizing those predicate devices or previously-cleared devices in your submission as part of your risk assessment, it's very helpful to point the reviewer to that submission and not just kind of use a trade name or something that wouldn't be identifiable.

And, in addition, a lot of times, there is not a great explanation of how representative test samples that are used are comparable to the actual final finished device and really not a discussion of any of those differences, how they could potentially impact the results. And lastly, I would point out that there is a lot of, I guess, difficulty sometimes using chemical characterization, and that was pointed out in the presentations. The methodology can be tricky, and it's not something that's widely accepted to use for addressing all endpoints.

So, I think, you know, things to be mindful of or include, be clear and comprehensive in the biocompatibility assessment. It's important that it's not an afterthought and that it's taken into consideration up front earlier in the project, and also to address all the recommended biocompatibility endpoints per the FDA guidance document. And really, if there are any gaps that remain, that you're not just glossing them over, that you are providing some evidence to address them.

MS. STAROWICZ: Great, great. Danese, when do you feel -- or when and how, I should say, can data be leveraged, particularly for existing devices, especially for devices with a long history of safe use? And when is it that new testing would be required, and how can manufacturers best take a risk-based approach and still address all the concerns?

DR. JOINER-FOX: So I think one of the differences between your new device and an existing device, for example, if it's a manufacturing difference or a sterilization difference are not expected to adversely impact any of the recommended biocompatibility endpoints, and you can provide that valid scientific evidence or justification for why new testing generally would not be needed. But it's important to encompass all of those things. You can't really skip any of that. This is easier if the existing device is manufactured by the same company.

However, FDA has provided some guidance on how one could proceed if the existing device was manufactured by another company. I think manufacturers can take a risk-based approach while addressing concerns, again, if an emphasis is placed on addressing all of those gaps within your risk assessment. It's certainly appropriate to leverage existing data, it's welcomed, it's what the guidance intends; however, it's not enough to just do that and leave it there. There are going to be gaps, we recognize that, and it's important to come in and fill them and then lead the reviewer in a way that it makes sense and they're not having to kind of scramble and interpret what you're trying to establish.

MS. STAROWICZ: Great, great. And what would you say -- back to 3-D printed devices. Any special considerations relative to showing the biocompatibility of a 3-D printed device?

DR. JOINER-FOX: Yeah, there's definitely some really great resources out there for 3-D printed devices; the technical additive guidance document is a good one, and then also using the FDA biocompatibility guidance is recommended. However, there certainly are

some specific considerations to think about. Additional material chemistry information might be needed, for example, a description of all material chemistry changes expected during the manufacturing of the device because your starting material could be exposed to partially melting and solidification processes at multiple times that could result in an unexpected or undesired material chemistry for some of the polymer systems. So that's important to think about. In addition, cleaning validation and discussion on if the material recycling could adversely affect the final device regarding biocompatibility, it is also very important to consider.

MS. STAROWICZ: Great, great. I'm just curious to know, have you had any experience with using master files for biocompatibility -- manufacturer, you know, establishing a master file for processing? And if you could share your experience in that area.

DR. JOINER-FOX: Sure. So, I do have experience with master files. I think they can be challenging. You know, it's important to really understand what is in the master file and how this can apply to your final finished device. And I know that's tricky when it's not owned by the company. It's maybe a supplier has this data, and it's not always clear that they'd be willing to share it. So sometimes it can be helpful to reach out to the supplier, and perhaps they can share how the master file data supports a finished device directly with the FDA, if they're not necessarily willing to do so with the company. I've seen some success with that.

But in my experience, really, the master file is often just a useful tool to establish the biocompatibility of the raw material, as either the company or some other vendor is conducting some post-processing of the material and, as you know, you have to look at all of that in your final assessment. So, you're still going to have to address how anything you might be doing with the material, once you receive it, affects biocompatibility for all of the

endpoints.

MS. STAROWICZ: Great points. They are great points.

Boy, time goes by really quickly with the panel sessions. I think we have about 10 minutes left, and with that, maybe I'll invite each of the panelists just to offer any additional comments, perspectives on the topic that our audience could benefit from. And maybe, Lisa, would you mind kicking us off?

DR. FERRARA: Sure. I think that the moral of the story is, especially the performance testing, making sure you assess the whole picture. That big picture puts together the entire story with respect to safety: Is this device safe? What are the potential risks? Have we addressed those risks sufficiently? Are we above and beyond what I call super physiological loads so that you're not trying to say, oh, our device failed that such-and-such of load? Well, to have it fail at that point, you're jumping off a building that's 20 stories high. So put things into realistic situations and apply that clinical relevancy to facts and look at the whole picture. Thank you.

MS. STAROWICZ: Thank you.

And Dawn?

MS. LISSY: I would add to what Lisa said as a foundation, and especially as we get into the arena of patient-specific devices, making sure that understanding the process that the FDA's going to ask for during that, of the volumes, the densities, the different shapes, that they're all addressed appropriately through all of the testing, and making sure that every -- again, the whole landscape of context, making sure that whether it's a small IBFD or possibly an SI-type device being patient-specific, wanting to make sure that we've hit all of the safety criteria and the foundational level and knowing what failure means, too, especially with -- again, I'm going to speak to additive manufacturing.

If you've got different porosities, there might be some artifacts in the actual

manufacturing process. Does that constitute a failure? And so those are good questions that I think we're going tackle on a regular basis here in the next couple of years.

MS. STAROWICZ: Great, excellent.

Danese, any final comments or thoughts on biocompatibility?

DR. JOINER-FOX: Yeah, just a couple. One is really just to emphasize, again, chemical characterization is a very useful tool, but it really does need to be done right and used the right way. So just echoing, you know, what was in the previous presentations. I've seen it both at FDA and on industry, the use of it is not always in the right way in the right mechanism, and certainly you want to make sure that we are doing it the right way and that it can be useful for the right endpoints.

In addition, I think a good biocompatibility assessment provides the right balance of necessary information. I've seen a lot of cases where kind of everything is thrown at the reviewer in the submission and kind of looking to see what may stick. I think a disciplined and clear assessment without the gaps that really is blocking the reviewer through what is necessary, available, and leveraged for each recommended endpoint will be most successful. And also, it's always helpful and appreciated from the FDA to hear what elements of our submitted assessments could be improved.

You know, I think that we're doing a lot of interaction, which is great and we really appreciate that, but within that interaction we'd love to keep hearing what are some of the major and minor deficiencies that we're seeing regarding the biocompatibility, especially as it relates to this interactive environment that we're in now, so we can continuously improve.

MS. STAROWICZ: Excellent, excellent.

Well, I see our time is coming to an end, and I wanted to thank all of our panelists. You have done a phenomenal job putting in so much content here in 30 minutes, which

does go by very, very fast. But I want to thank Lisa and Dawn and Danese for giving all of us these great perspectives on mechanical performance testing and biocompatibility. These are areas, as we all know, that are hugely important for orthopedic device submissions, and they're often associated with significant costs and time for manufacturers, so we want to get it right the first time. So, I really appreciate you all being here and imparting your knowledge and words of wisdom. So, thank you very much.

DR. FERRARA: Thank you, Sharon.

MS. LISSY: Thank you.

DR. JOINER-FOX: Thank you.

MS. STAROWICZ: All righty. I think, at this point in the program, I'm going to turn it back to Ronald, Colin, and Brent to lead us in another general Q&A session to address any questions that have come in. Hopefully, there have been a lot of questions coming in throughout the day for FDA.

And I do have one question maybe, if I may, to start off the session, and that actually pertains to ORCA. This is something we just talked about in the prior industry panel session, and my impression is that this has been really received very favorably from industry. And I'm sure you're asked this all time, but does -- you know, is FDA planning to do -- you know, expand the performance criteria data publication to other product areas, and if so, do you have a sense of what the timing might look like on that?

DR. JEAN: That's an excellent question, Sharon. I would start out by saying that, you know, just to give a history about ORCA, this started as a collaboration with our premarket group and the FDA's Office of Science and Engineering Laboratories employees with Dr. Anton Dmitriev. And Jonathan Peck was kind of the founder, if you would, of this collaboration, and the original feasibility study was very successful.

And so within OHT6, under Captain Peat, ORCA has received a lot of support, and

Jonathan has managed, with a whole cadre of team members, to really expand our footprint within this area. So, I think the best person to answer your question and really, the person who should be talking about ORCA and sort of where we've been, as well as future directions, is Mr. Jonathan Peck. So, I'd like to turn over to him to give you a little bit more information on this.

MS. STAROWICZ: Great.

MR. PECK: Thanks. Thanks, Ronald. And thank you, Sharon, very much for this question.

Just to take a step back to define ORCA a little bit. What it is and what it's been is essentially a set of databases that we've created and been populating with design and mechanical testing information from some of our higher-volume 510(k) areas. In fact, we're just wrapping up now another very successful summer of data entry with another great set of summer students, actually, and we are -- the data is essentially immediately useful for internal comparisons for FDA reviewers. But that is sort of what's also been behind our ability to aggregate and de-identify some of this information and then put it out there for public consumption. And I was thrilled to see the Menti survey responses that -- you know, the awareness around it and that it's well received.

So Kate Kavlock earlier hit on the two papers for cervical and lumbar cages, and as a future direction there, the scope of those initial papers was limited to traditionally manufactured monoblocks, single-piece cage designs, and in the spirit of keeping up with where the industry is going with these, Kate is now leading an effort to collect data on aggregately manufactured cages and integrated fixation cages. And, you know, the goal there is not necessarily to put out more published data, but to do internal comparing and contrasting of devices' different technological features. And maybe the outcome of that will be hey, we can utilize this currently published data as acceptance criteria for these

other devices, as well.

In that same vein, we're currently working on a paper with previously collected data for thoracolumbosacral pedicle screw systems, and that's in the works. And just this summer, we collected a lot of great data for occipital cervical and cervicothoracic screw systems. We've got our fingers crossed. You know, they're a little lower volume than the thoracolumbar systems, but we've got our fingers crossed that, that will lead to a paper, as well.

I've got a bunch of things I'm excited about, so bear with me. But there's also the safety performance pathway that's another great mechanism for us to utilize this data for the generation of acceptance criteria. That's a new -- relatively new 510(k) pathway for industry, and what it involves is FDA putting out device-specific guidance documents that actually include acceptance criteria for all the tests that you need to do for a device that fits the scope of that document.

I think we're pleased to say, I just got word this morning, that the first two guidances have gone final from the Center in that area. They're not orthopedic yet -- they're for conventional Foley catheters and cutaneous electrodes for coring purposes -- but there are two orthopedic documents that are draft right now, and I was again pleased to see the awareness around the safety and performance-based guidance for the anterior spinal plating systems.

And I'll say that, while you can't submit a 510(k) for those devices under the safety and performance-based program until they're final, you can certainly reference that data as your acceptance criteria for one of these devices in another 510(k) pathway that's currently available.

And I will say that Chris Ferreira -- outside the spine in orthopedics, Chris Ferreira has also -- the drafting of a non-spinal fracture fixation screw guidance document that falls

into that pathway as well, it's out for draft, and we got a couple more in the pipeline that I can't mention yet.

And lastly, as another mechanism, we've been working on a standard with ISO that's currently out for public comment. It's ISO 23089, and it's on the mechanical performance or mechanical performance testing for spinal cages. It aligns really well with the recommendations in FDA's guidance for these devices, and it also utilizes our published data as recommended or optional acceptance criteria. And that's one thing I really want to reiterate here, that these are all optional acceptance criteria. You always have the option to revert back to side-by-side testing, if necessary, but these are -- this is more information I'm trying to put out there.

And lastly, I just want to make the point that we really -- for this to work, we have to have some confidence that the test methods result in results that are comparable across labs. If not, it doesn't make any sense for us to be aggregating and putting this data out there. So we're really kind of trying to start it with some of the standards that we're most comfortable with, the device area that we're most comfortable with. We also need enough volume in these product areas to pool enough data together to aggregate, de-identify, and put it out there. But with those kind of factors in mind, we're very open to any suggestions anyone has for future areas of data collection that we should engage in.

So, thank you so much for the opportunity to comment on this.

MS. STAROWICZ: Great, great. I know it's a huge effort, but very well received. I'm looking for some more in the future. So, thank you.

And I'll turn this back to all of you to continue with the audience questions.

DR. JEAN: Sure. I think we'll start off with Colin and let him jump into the next question.

MR. O'NEILL: Yeah, I've got to unmute myself. So I think there were a few questions

that came out of the morning session that, you know, I can jump into. There are several, but I think three of them all sort of relate, so I'll do those consecutively.

The first one is: Can you clarify how FDA determines the intended use of a device? Intended use and indications for use seem to be used interchangeably.

So, my answer to that is intended use is a description of what a device is designed to do and how it treats the patient. Indications for use is a description of what patients or which condition the device is treating. For example, a spinal device may be intended to provide fixation and the mobilization as an adjunct to fusion, whereas the indications for use would be for patients with degenerative disc disease, stenosis, trauma, et cetera. And I appreciate that it can be confusing, and many of our indications for use statements include a lot of intended use language and much of the intended use language is important so as the scope of the device, the historical precedents, and the evidence for how the device is to be used on label can be stated.

So, going into the next question that's related, the question is: If the intended use of your predicate is not clearly stated, but the product code for your device is the same, is it safe to say that the intended use is the same?

So, product codes are generally used by the FDA to differentiate devices where we may need to categorize them separately for easier postmarket surveillance and tracking internally. Intended use is something that's evaluated early on in the 510(k) decision-making flowchart. And in order to -- for a predicate to be a valid comparator to a subject device, it must have the same intended use. So, product code assignment does not directly relate to only intended use, but I cannot give you an example where there are two devices with the same product code and that have different intended uses.

So, to answer the question, in general, yes, I think it's safe to say that two devices of the same product code would have the same intended use. However, they're not directly

related, or product codes aren't assigned just only to a -- in an intended use.

So, the third question in that category is -- and I think this goes back to cross-compatibility between components or devices from different manufacturers. The question is: Is the major issue in indicating/claiming compatibility to the question of whether the device changes the indications for use with a compatible device?

So, changes in the indications for use would be one component of our concern with device compatibility of devices or components from different manufacturers. I would say the main concern is, in general, for compatibility of many aspects. For example, one device's quality system or device design can change, and that would potentially affect the device or components it's intended to be compatible with. So one thing we ask for in that situation is agreement between the manufacturers, and knowledge of this agreement that they will communicate about any future changes can help mitigate concerns to the -- so yeah, that's -- do any of the other -- Ron or Brent, do you have anything to add to that or go on to another question?

DR. JEAN: Yeah. I think one other thing we didn't mention this morning related to compatibility is, as many people in the spinal device sector are aware, a lot of companies restrict the use of their product in the labeling to only other components that are manufactured by the same company. So that is also a limitation that companies looking to sort of establish some cross-compatibility with another spinal device component run into.

But no, I think you laid it out very well. You know, it's still helpful within a 510(k) submission, even if you're referencing a product code and referencing a regulation, to still describe explicitly sort of what -- you know, how your device works. We have a spinal 510(k) guidance. We're looking for clarity on how your device is used, looking at illustrations or models of this, and again, the better you can connect with how your device is going to be used, especially if there is a novel or new design feature that we don't always

see, the better the reviewer is going to be able to ask the right line of questioning faster with you. So, I would recommend not leaving that very ambiguous.

Brent, did you have anything else on the topic?

DR. SHOWALTER: No, I don't have anything to add to this, but I can move on to the next question, if we're ready.

DR. JEAN: Yeah.

DR. SHOWALTER: All right. So, this question states: The use of FDA for a submission to develop -- sorry, to demonstrate a device worst case for a device verification and validation. So the question is actually: Does the Agency recognize the FDA or prefer a mechanical rationale demonstrated in the submission?

So, I think this touches on a topic that was brought up in the mechanical testing presentation earlier right after lunch, but the short answer is we definitely look at FDA when we're determining worst case. So, I would separate out a determination of worst case into kind of three categories, right, with the most basic and preferable method, if you can, is to use an engineering rationale or a mechanical rationale.

So if your device is simple enough that you can use the smallest diameter, for example, for a pedicle screw, if you've got the smallest diameter, there's no other odd features, or if you've got a monoblock cage and you're looking at the smallest footprint -- those kind of rationales, if you can make them, are the easiest for us to understand, easiest to make, and therefore, we would prefer to use those over finite element modeling.

However, there are some designs where that doesn't make sense, right? So if, for example, in a cage there are lots of internal features that make the cross-sectional analysis difficult where different windows change as the footprint changes over -- the windows change as the footprint expands and things like that, those are the cases in which finite element modeling is really useful. So, it's really useful to be able to identify the locations

that probably expands the highest stresses.

And in conjunction with this, there are two really helpful documents to kind of point out what we expect to see in the reports describing the FE studies. So, the first is a guidance document, it's entitled Reporting of Computational Modeling Studies in Mechanical -- sorry, in Medical Device Submissions. This is a fairly recent guidance document, and I believe it came out about two years ago or so. There's also a document that's not put out by us; this is an ASME document, it's entitled ASME V&V 40-2018, called Assessing Credibility of Computational Modeling through Verification and Validation: Applications to Medical Devices. So, these two documents go into a lot more detail about things like -- things that you should describe in your report with finite element modeling, so things like how you select your mesh, your elements, your constitutive models, all of the little details that go into making a finite element analysis successful. So those are the things that we definitely look at. We use them all of the time in determining worst case.

Where we've noticed that the finite element modeling isn't quite as useful in determining worst case is when there are multiple components. So, it's very, very tricky to describe the boundaries between subcomponents, things like expandable cages or sometimes for pedicle screw systems. When there's lots of different components that are made together, that finite element modeling is very difficult to do well and to validate. So, in those cases, sometimes we may -- it may be in your best interest or we may request to do a couple confirmatory tests to determine what the worst-case device may actually be.

And with that said, we would also like to point out that there is currently a work item in ASTM, so this is ASTM WK64097. So, this is specifically for developing computational modeling practices for spinal fusion cages. So, it's something that's -- it's a work in progress. We're still -- ASTM is still working on it, but this might be something that you might want to look into as -- in developing recommendations and for determining worst

case of cages.

Ron or Colin, do you have anything to add regarding finite element testing? All right.

MR. O'NEILL: That was a great answer in summary, so I don't have anything to add.

DR. SHOWALTER: I'll pass the baton on to Ron.

DR. JEAN: Okay, the next question we're going to be talking about is shelf life. So we received a question, it says: I'm interested in understanding the shelf-life requirement for medical devices that are considered sterile.

And so, I think, within orthopedics, it's not very often, but shelf life is something that you need to consider in two ways. For example, if you have -- let's say you have a specialized coating, you know, there's the aspect of the sterility and the ability to provide a sterile barrier for a certain amount of time, but then there's also a performance issue. So, if you have a coating or some other material that potentially is degradable and has some stability considerations, your sterile barrier may last longer than the composition of the actual material itself to be able to perform its function as intended or as tested at time zero. So I would say that, within orthopedics, both of those things need to be considered when you're looking at labeling and shelf life, and definitely you should provide testing in both of those arenas.

Now, the second part of the question is: Also, could you please let me know how is the shelf life evaluated? Is it on the packaging or the product? So, I'm going to turn this over to our sterility expert, Mr. Steven Turtil, to sort of address how -- some of the technical considerations of shelf life.

So, Steve, it's all yours.

MR. TURTIL: Sure, thank you. So, the primary go-to standard for packaging is ISO 11607. There's a Part 1 and a Part 2 to it, but in both of those it refers to performance testing and stability testing. Performance testing is how well the package is going to

maintain its sterility during shipping and handling, worst-case shipping and handling. But what we're talking about here is the stability testing, which is the shelf life, and that is -- that 11607 series actually identifies a number of different ASTM standards that are very helpful. But basically, what we like to see is accelerated aging or real-time aging followed by a seal strength type of test, and that's basically the way we look at it.

If you do accelerated aging, we're perfectly okay with that for a clearance, but we also want to know that you've initiated real-time aging at the same time and you're doing that in addition, just to confirm -- as confirmatory testing for the accelerated aging simulations. And it's really up to you. You can -- I think it's ASTM F1980 which will actually give you the accelerated aging calculations, so it's up to you how long you want to test out for, what sort of shelf life you want to determine for your product. Do the math, carry it out to that position, and then go ahead and do your seal strength testing after that. That's the basics of it, yeah.

DR. SHOWALTER: Thanks for your comments, Steve.

So, I'll turn it over it over to Colin to address the next question.

MR. O'NEILL: Yeah. There was a follow-up question on the intended use and indications for use from our earlier question set, and the question is: When does a change in indications for use result in a change in intended use? For example, if an imaging system is changing anatomy, for example, a neuro or ortho or an ENT device, does that result in a change of an intended use?

So, if I'm interpreting this question correctly, a change in indications for use doesn't necessarily mean a change in intended use. The way that the device either assesses or treats the patient may not change, but the condition -- the patient condition or the type of condition that it does treat can change. So, they're decoupled a little bit in that sense. But sometimes a change in conditions for use does change the intended use because the

condition is so different that the mechanism of treatment needs different considerations.

So that's my answer to that. I have another set of questions that relate to the morning, but I wanted to give Ron and Brent a chance to step in to answer that question, if there are any additional comments.

(No response.)

MR. O'NEILL: No? Great. Okay, so two more questions. They relate to predicate devices: primary predicate devices, additional predicate devices, and reference devices. The first question is: Can you kindly elaborate on the difference between the use of a predicate device, a secondary predicate device or devices, and a reference device or devices in a 510(k)?

So, the terminology we use are a primary predicate device, additional predicate devices, and reference device. So, in order for a 510(k) to be walked down the 510(k) flowchart for determination of substantial equivalence, it needs to be compared to a single primary predicate. The primary predicate should most closely match the subject device in terms of the indications for use statement, device design, and the performance evaluation.

Now, additional predicates can be used to compare and mitigate concerns related to other aspects of 510(k) evaluation and predicate comparison, such as noting that the manufacturing processes are the same to address biocompatibility concerns. Sometimes additional predicates are used for performance comparisons, as well, but the primary predicate should be the most applicable predicate where the best comparisons can be made. Additional predicates, when necessary, can fill in the gaps where the primary predicate does not provide that type of comparison for that aspect.

Reference devices can be utilized where there is a need for setting up a predicate in another classification regulation to support comparison to the subject device. For example, if a novel material was utilized in another device from another classification, the applicable

evaluation for the subject device may still be necessary depending on the situation; however, relevant information on the reference device may minimize necessary validation on the subject device.

So, the next part of the related question -- the other question that's related to this is: During a 510(k) application, besides the primary predicate spine device, can a reference device taken from a non-spine application be indicated for a new spine application?

So, it's a little tough to deal with hypotheticals without concrete examples in writing, but changes to the indications for use, as long as they do not change the intended use or raise different questions of safety or effectiveness, can be made under a 510(k). Theoretically, reference predicates may support the requested change in indications for use, although I can't imagine a situation where a reference device would have an applicable -- applicable information to support new indications for use of a device with a different intended use and/or one that raises different questions of safety and effectiveness.

In cases where expanded indications are sought, a reference predicate may not be necessary if new indications are supported by adequate evidence or rationale. However, I don't want to discount that there may be a situation where clinical data from a reference device may help support changes in indications for a device from a different classification regulation. However, again, devices under different classification regulations generally have different intended uses, so the information may not be relevant to the subject device or possibly not containing poolable data with the subject device.

So, Ron, it looks like you have something.

DR. JEAN: Yeah, yeah. I mean, I think you did a really good job covering that, but it's worth sort of really emphasizing to everybody that a primary predicate device is a device that you walk all the way down the flowchart, and there are many situations when you're submitting a 510(k) where all you need is a primary predicate device. You don't need any

additional predicates; you don't need any reference devices. But, again, you have to be able to walk through performance data, and potentially, you could walk all the way to an SE decision with a primary predicate.

You know, the other consideration is really to emphasize, especially when you're bundling a 510(k) submission, that you can only have one primary predicate device per submission. And really, a good example of this is the fenestrated screw and cement combination that the Division of Spinal Devices cleared a number of years back. So it was a very special scenario of bundling two products within a 510(k) submission. You know, these were based on the same clinical dataset and literature, and so we were receptive to that particular bundling scenario. However, we didn't have a primary predicate for the cement and a primary predicate for the fenestrated screw set, and we actually have to pick one, which we elected to sort of select a cement predicate, and then we just used an additional predicate to walk the screw set down the 510(k) flowchart.

Again, that's a very unusual scenario, but the point is just remember, primary predicate, you can only have one per submission. And primary predicate is something that, if you can walk all the way down the flowchart with just that, you will save a lot of confusion for the reviewer if they can just focus on that one particular predicate and get all the way down to an SE decision.

And that's all I had. So thanks, Colin.

MR. O'NEILL: Thanks.

DR. JEAN: I think we can turn it over to Brent.

DR. SHOWALTER: Yeah. So, I have -- I'm going to take the conversation in a very different direction. So, this question says: What are FDA's data expectations for spinal cages indicated to be used in conjunction with 361 HCT/Ps, such as demineralized bone without excipient; cortical bone chips; cancellous bone chips; and bone chips with native

viable cells, meaning the tissue is minimally processed to retain the native highly endogenous cells, no cells are added? The question continues: I am aware of cages cleared to be used with 361 HCT/Ps but curious on the data requirements for the allografts and allograft compatibility with the cage. The cage and allograft are not shipped as a kit, and the cage is shipped from the device manufacturer to the hospital, and the allograft is shipped from the tissue bank to the hospital.

So, this answer may disappoint a little bit, but I'll give the bad part first, and then I'll expand a little bit more where I can. So, classification of HCT/Ps per 21 C.F.R. 1271.10 is not under CDRH's jurisdiction. So, this is under CBER jurisdiction, and as a result, we are unable to make many comments on whether any specific propriety allograft product, such as those processed to retain native viable cells, are regulated solely under Section 361 of the PHS Act.

So, I'll get back to that in a second, but I do also need to recognize that, within our indications for use for cages, there are -- as people are well aware, there are a number of cages that are cleared for use with allograft. And we recognize that the term allograft can be used in a wide range of definitions, right? So, I've seen some submissions where they'll have eight to ten different classifications of what they would potentially consider to be allograft. But as used in the indications for use in spinal devices in particular, it's why we specifically state that allograft is for cancellous or corticocancellous bone for most of the devices that we have. And the reason for that is that these -- I know that these particular clearances were done based on literature data of this. Also, these clearances don't mean that the allograft comprised of the cancellous and/or corticocancellous bone graft is inclusive of all types of allograft, right?

So back to the initial part of the answer where I said we can't comment too much on this. We do recommend that anyone who wishes to co-promote their cleared intervertebral

body fusion devices for use with a propriety allograft seek clarity of the regulatory status through the pre-submission program. Actually, I should amend that. I'll give you the contact information of the individuals who are actually responsible for this.

So, the main contacts for this is the Tissue Reference Group, also called the TRG, and they're in charge of the classification with allograft products as 361 HCT/P. So, their phone number is -- I'll repeat this twice. I know I'm going a little bit fast. But the main contact for this is tissuereferencegroup@fda.hhs.gov, where there's also a phone number, 240-402-8278. So, once again, the people you can direct these type of questions to are tissuereferencegroup@fda.hhs.gov, or to the executive secretary of the Tissue Reference Group, which is 240-402-8278.

And so, just in closing, we are open to expanding indications to use with 361 projects, such as demineralized bone graft without excipients with appropriate clinical literature. And if you want to do that for your particular project, we recommend that you submit a Q-Sub with the indications that you're seeking and also the type of information that you have or intend to achieve, obtain, to support it.

So, with that, that's all I have for that question. Ron or Colin, do you have anything to add?

MR. JEAN: No, I think that was an excellent response, Brent.

DR. SHOWALTER: In that case, I'll turn the ball over to you, Ron.

DR. JEAN: Sure. So, I think, in terms of timing, we're looking at the inbox and what we can potentially address. You know, it looks like there is maybe one or possibly two more questions. I did want to mention that, with respect to -- just a comment really quickly. You know, Lisa Ferrara had an excellent point in the discussion about looking at the big picture, and I think that that's a really important point to consider.

Because, just anecdotally, we've seen a scenario where a company had a device that

wasn't quite similar to a predicate, but they did all the testing and they're like, see, the testing basically is just as good if not better than the predicate device. But the unfortunate problem is the product couldn't even get down the flowchart. There really wasn't a predicate device for the product. So, you really do have to consider the big picture. You know, there is a lot of experienced consultants out there, and there are also excellent staff at FDA that are ready to sort of interact with you as we can, you know.

And then just one other thing that I wanted to get in is related to just some of the paradigm shifts that we're having. You know, with respect to ORCA, you've seen that we're trying to be more progressive and actually have benchmarks that you can all compare against and maybe save time and effort in terms of doing the side-by-side testing where it's applicable. But I think another area that we really, really added a lot of -- sort of covered a lot of ground in the last few years since we've been OHT6 is with respect to real-world evidence. I think this is something that you're seeing a lot more, again, leadership in this within our orthopedic group. We've had an ortho CRN meeting. You know, I'm definitely sure there's things in the works for the near future. But again, real-world evidence is something that's not going away, and we're very interested, invested in sort of exploring this and see what data we can leverage to move the needle forward in terms of future clearances or even refinements of labeling.

And I did cheat, there's actually a third item I want to really discuss, and it sort of carries from this morning, related to TPLC. Again, now that we're at TPLC organization -- and I think there was a question that actually came in the inbox related to, you know, how do we look at postmarket data now and feed that within the premarket space. And I think that's, that's an excellent question. We look for trends and we look for problems for the most part, and if we see a product area where we're starting to see a signal, we may ask some additional questions just to get ahead of the problem. And then we may follow up

with the existing products and see what can be done or whether this is truly a solid signal or not.

And I think in the same way, you know, down the road what you'll likely see is, once we develop a comfort in a certain product area, you may have opportunities to sort of re-temper and recalibrate where we set those benchmarks. And I can say for a historical fact, we've done this in the spinal space with an example, you know, pediatric posterior instrumentation for adolescent idiopathic scoliosis. At first we were very careful, very concerned, and very cautious in the rollout, and we were able to pull that back a little bit when we were -- you know, when we had 100 or 120 clearances under our belt and we had a lot more comfort and familiarity and there was a good marketing track record in addition to the historical literature.

So, I'm sorry for jumping in, Colin and Brent, but these are points that I think are of value just to understand better sort of the direction that we're going in within the new structure of the organization.

DR. SHOWALTER: Thank you very much, Ron. If you don't mind, I'll add a little bit to that.

So I would say that the premarket requirements aren't changing as a result of shifting to the TPLC environment, right? A 510(k) is still a 510(k). But as Ron mentioned, I think his example of real-world evidence is a really strong example of how we're trying to use this postmarket data that we're seeing a lot more of. Now that we're in charge of both, we're trying to use that to guide regulatory products and ideas going forward, right? So we have -- you know, as Ron mentioned, we're looking at MDRs and trying to see if there are any signals and using that to guide or tease out if we should be developing new test methods.

So those Menti questions that I asked earlier about if you have any ideas about what

kind of guidance documents or test standards that we should be looking into, you know, we're asking those questions with a lot of different data in mind, right? And so another one of them is the postmarket data that we're seeing more of. So, we're trying to look at all of the information that we have available and find more data sources so that we can provide relevant guidance and feedback for future submissions.

MR. O'NEILL: Thanks, Brent.

I'll just add a few things to that in terms of -- in addition to those additional data sources and real-world evidence, you know, what the TPLC structure allows us to do where our close-knit teams are now reviewing EIRs and recalls in addition to premarket and postmarket surveillance, MDRs and such, we are able to act with more precision and a least burdensome bar for making corrections from, say, a current recall, and then we get a corrected fixed submission.

We have a better -- we have a jump on the understanding of the root cause, you know, and the CAP (ph.) evaluation and how that product is going through its life cycle and how things are being evolved and corrected. So that's the real advantage, I think, that we have in our new structure, and I'm hoping industry can see dividends for that for our increased understanding of how devices evolve and quicker understanding and quicker actions on our part.

DR. JEAN: Okay. So, I think we've gone a little bit over. Our apologies. But, at this point, I will turn it back over to Sharon. Thank you.

MS. STAROWICZ: Great. Excellent. Excellent Q&A discussion. Thank you very much.

Well, this brings us near to the end of the day here, and I wanted to -- before turning the program over to Dr. Jean for some closing remarks, I just wanted to express my gratitude to FDA for hosting this workshop. I know these types of programs don't happen by accident, and I know there's significant effort and time that went into making today

possible. So, I really wanted to thank all of the FDA speakers, the industry panel participants for sharing their guidance and their expertise.

And I think it's fair to say we all share common goals of having -- you know, we want to have comprehensive and complete submissions that address relevant safety and effectiveness questions and do so in a manner that utilizes both the FDA resources and the industry resources in the most efficient manner. So, today's workshop really has offered many practical ways for us to achieve these collective goals.

So, thank you again for your attention, and it's my absolute pleasure to join you today. And now over to you, Ronald, for closing comments. Thank you.

DR. JEAN: Thank you. So, I really appreciate your attention and participation in today's workshop. You know, we're at the end, we've done it, we've managed to walk through the major sections of a spinal device 510(k) submission. And I know there's a lot to absorb, but as you've heard, the good news is you'll be able to go back and revisit some of this material in more depth if you need to.

So, again, you've heard a number of talks from FDA staff, and you've listened to feedback from highly experienced industry professionals, and all of this has been aimed at helping you prepare a high-quality 510(k) submission. You know, these tips should also help you avoid issues that could lead to unnecessary delays. So, we really tried to add value and really give you some pearls here so you can avoid pitfalls that we've seen in past submissions.

I really appreciated the great discussions and questions that we had today. You know, the Menti feedback was very informative. Going back to the very first session, it sounds like there are areas of improvement we can explore. You know, we would like to see consistency or at least a perception of consistency across all of the divisions within OHT6: Office of Orthopedic Devices.

And there were quite a few questions we received related to device description, and I really hope that our presentations and the discussions with the industry panels and the individual responses to the questions help address these concerns. So, it's the intention of OHT6, the Office of Orthopedic Devices, to be a world-class leader in the regulation of orthopedic devices, and activities like this workshop really help us achieve this aim.

You know, I'm really thankful to Captain Raquel Peat, our office director. Her vision and her support really made this event a reality. And I'm really grateful to all of the FDA staff for the time out of their busy schedules, because we have not slowed down with the summer and have provided you with valuable 510(k) tips, and that includes Dr. Zane Wyatt, Ms. Brittany Ferrell, Mr. Charles Warner, Mr. Aakash Jain, Mrs. Vikansha Dwivedi, Dr. Aprajita Garg, Dr. Anne Talley, Mr. Steven Turtil, Dr. Katherine Kavlock, Mr. Jonathan Peck, and of course, our assistant directors within spine, Mr. Colin O'Neill and Dr. Brent Showalter. But in addition to them, you know, we had a lot of support within the group, and I'm really thankful to the others who contributed to this, including our spine teams and Ms. Nicole McDenny (ph.).

So, today, you've also had the privilege of hearing from some of the top professionals in their respective parts of the medical device industry ecosphere, and I'm extremely grateful to have had Sharon Starowicz serve as our MC for today's event. And you have heard from Ms. Alexia Haralambous, Dr. Allison Komiyama, Dr. Caroline Rhim, Dr. Kelly Baker, Ms. Janice Hogan, Mr. Glenn Stiegman, Dr. Lisa Ferrara, Dr. Danese Joiner-Fox, and Ms. Dawn Lissy.

So sometimes with productions like these, people hard at work behind the scenes are forgotten, but we're not going to let that happen today. You know, Lieutenant Commander Ogochukwu Ogoegbunam, one of our OHT6 regulatory health project managers, has been really instrumental in being the liaison and interfacing with everybody

involved in the day's production, so I really owe her many great thanks.

And, you know, we're extremely fortunate to have had the help of the FDA TV Studio staff. They do so much work behind the scenes, both in the preparatory planning of this event as well as watching every minute of today to make sure everything ran smoothly. So, I want to thank Ms. Barbara Richards, Mr. Chad Heupel, as well as all the others who really made this event go very smoothly.

And lastly, I'm very thankful for you, the audience, for taking the time to participate in today's event. Captain Peat mentioned that we had over 400 registered participants, but based upon our last count this morning, it skyrocketed to over 645 individuals registered. So that's more than we could have ever expected for an in-person event and, you know, we're really thankful for your participation, and hopefully you got a lot value out of this.

So as this workshop draws to a close, I'd like to briefly mention where we go from here. So, hopefully, you take some of the practices that you've heard today, put those into action as you prepare 510(k) submissions, and share these tips with your colleagues or at least share the links to the materials once they're available. You provided us with very insightful questions. We tried to address the ones that are of the greatest interest to the audience, but there's more than we could address in the limited time today. And so, it's our plan to produce a white paper in the not-so-distant future that provides responses where we're able if there's enough content.

And further down the road, you know, we don't want this to be an *n* of one. We'd like to have more workshops within OHT6: Office of Orthopedic Devices, and if you have any comments about today's workshop, you know, we appreciate that, or ideas to make future events even better. So, don't hesitate to contact us at OHT6-Feedback@fda.hhs.gov.

In addition, I just want to point out to everybody who registered for this event that we'll be sending you a survey with some focused questions, and we hope that you take a

moment to respond. So, again, thank you to everybody for your time today. I wish everybody a great afternoon and a safe and wonderful time as summer draws near. Be safe and be well. Thank you.

(Whereupon, at 3:50 p.m., the meeting was adjourned.)

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C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

PUBLIC WORKSHOP - SPINAL DEVICE PREMARKET REVIEW

August 13, 2020

Via Webcast

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

_____/ S /_____
TOM BOWMAN
Official Reporter