UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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# VIRTUAL PUBLIC WORKSHOP - ORTHOPEDIC DEVICE POSTMARKET REVIEW

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Via Videoconference

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M E E T I N G

(8:30 a.m.)

DR. PEAT: Good morning, everyone, and thank you very much for joining the Orthopedic Device Postmarket Review Public Workshop.

My name is Captain Raquel Peat, Director of the Office of Health Technology 6, which is the Office of Orthopedic Devices in the Center for Devices and Radiological Health.

This meeting is occurring during unprecedented times. The COVID-19 pandemic has challenged all of us for over a year. For FDA, that has meant tirelessly working to help bring diagnostic devices, personal protective equipment, and therapeutics to patients as quickly as possible. Our staff across the Center are very busy with COVID-related work, as staff in the Office of Orthopedic Devices have been assisting other offices with COVID work while equally maintaining our orthopedic premarket and postmarket work activities.

Last year we held a public workshop, the first virtual workshop in the Center during the pandemic, that discussed spinal device premarket review and in an effort, this spinal device premarket review workshop was held to be more transparent in enhancing public understanding of FDA's review of data and information submitted to support premarket authorizations for spinal devices.

We gather today in this public workshop to share knowledge pertaining to FDA's postmarket programs and activities in the regulation of orthopedic devices.

A main reason for these external collaborations is to enhance CDRH's mission, which is to protect and promote the public health. In our mission, we are to assure that patients and providers have timely and continued access to safe, effective, and high-quality medical devices and radiation imaging products. We facilitate medical device information by advancing regulatory science, providing industry with predictable, consistent, transparent and an efficient regulatory pathway, and assuring consumer confidence in devices marketed

in the United States. While supporting our mission, the vision of our Center is patients in the United States have access to high-quality, safe and effective medical devices of public health importance first in the world. Therefore, patients are the heart of what we do each and every day as public servants.

As the Center for Devices and Radiological Health makes way through the total product life cycle, also called TPLC, and in our transformation as a TPLC office, we would like to share our experience of well-rounded regulatory programs that impact TPLC. Our Center's effort to create a cycle of knowledge in premarket to postmarket that includes compliance and surveillance back to premarket would result in improved medical devices based on real-world evidence learned through the devices' life cycle.

The objective of this workshop is to provide an overview and description of the requirements related to recalls, medical device reporting, post-approval and postmarket surveillance 522 studies and postmarket approval reporting, as well as FDA's inspection. The main objective of this public workshop is to improve public understanding of medical device postmarket programs and requirements related to orthopedic devices.

Throughout the day you will hear directly from the review staff from the Office of Health Technology 6, the Office of Orthopedic Devices, the Office of Regulatory Programs, and the Office of Clinical Evidence and Analysis, as well as industry perspectives. Presenters will discuss potential strategies to address challenges in these areas, and ongoing analysis and trends, to allow transparency into FDA's processes and decision making to better aid orthopedic device stakeholders to strategize and implement various corrective actions and design changes. I hope that you will find our presentations and discussions informative and that it will serve as a platform to promote and protect public health.

I would like to acknowledge the outstanding leadership of Dr. William Jung and thank the entire FDA team, including staff from the Office of Orthopedic Devices, the Office

of Clinical Evidence and Analysis, the Office of Regulatory Programs, and the Office of Communication and Education, in particular, FDA studios and other FDA contributors. In addition, we are grateful for the contributions of our external collaborators and we greatly appreciate your attendance and participation in today's meeting.

I would like to introduce Mr. Jon Speer, who will be the master of ceremonies today to facilitate our presentations and discussions. Jon Speer is both the founder of Greenlight Guru, a medical device quality management software solution, and a medical device guru with over 22 years of industry experience in a variety of roles including product development, project management, quality and regulatory. Jon knows the best medical device companies in the world use quality as an accelerator. Jon is a thought leader, speaker, and regular contributor to industry leading publications like *MedTech Intelligence*, *Quality Digest*, *MD+DI* and more, in addition to his contributions of hundreds of free content resources.

Thank you, Jon, for your willingness to participate as MC for today's event, and I will turn the meeting over to him. Thank you and enjoy the rest of the meeting.

MR. SPEER: Thank you, Captain Peat, for that introduction and kind words. And good morning to you all and welcome to the FDA orthopedic device postmarket review workshop.

My name is Jon Speer and I am the founder of Greenlight Guru. I've spent my entire professional career in the medical device industry in various roles ranging from product development to quality to regulatory, and I am honored to be the master of ceremonies for today.

Let me give you a brief background about today's workshop. This workshop is intended to enhance public understanding of FDA's postmarket activities related to the regulation of orthopedic devices under 21 C.F.R. Part 888. The purpose of the workshop is

to share information with stakeholders, including members of the orthopedic community, device manufacturers, regulatory affairs professionals, clinicians, patients, and the general public on FDA regulations, guidance, and programs related to orthopedic device postmarket activities and challenges that are commonly faced in this area. This public workshop seeks to share knowledge pertaining to FDA's postmarket programs and activities in the regulation of orthopedic devices.

The goal is to provide an overview and description of the requirements related to recalls, medical device reporting, post-approval and postmarket surveillance studies, inspections, and postmarket approval reporting. The main objective of this workshop is to improve public understanding of medical device postmarket programs and regulatory requirements related to orthopedic devices. This workshop considers the role of benefit and risk in FDA decision making and mitigation measures for minimizing these risks. The public workshop is not intended to communicate any new policies or processes.

The topics for discussion will include recalls, MDRs, post-approval and postmarket surveillance studies, inspections, and postmarket approval reporting. Presenters will discuss potential strategies to address challenges in these areas and ongoing analysis and trends to help orthopedic device stakeholders strategize and implement various corrective actions and design changes.

We will have three sessions throughout the day and each session will have contributions from FDA and from industry, as well as a group discussion. Session 1 covers recalls and medical device reporting, Session 2 covers post-approval studies and postmarket surveillance studies, and then Session 3 will cover inspections and postmarket approval reporting.

Let's dive into Session 1. During this first session, several speakers will be covering aspects of recall and medical device reporting. Our first presenter will be covering recalls

overview and requirements and will be presented by Danielle Cristino of the FDA. Dr. Cristino has been serving as the lead reviewer in the Division of Joint Arthroplasty Devices within the Office of Health Technology 6 at FDA since 2020. She holds a bachelor degree in mechanical engineering with a concentration in bioengineering from Rowan University, and a Ph.D. in biomedical engineering from Virginia Tech. Dr. Cristino is a staff fellow with expertise in injury biomechanics and mechanical testing of orthopedic implants. She has experience reviewing various joint arthroplasty devices for both pre- and postmarket submissions.

DR. CRISTINO: Good morning, my name is Danielle Cristino and I'm a lead reviewer on the Shoulder Arthroplasty Devices Team in the Division of Joint Arthroplasty Devices in the OHT 6.

We'll begin with an overview of recalls and their requirements. This presentation serves as a refresher of recall contents and the recall process. I'll begin by defining what a recall is. I'll also discuss when to report a recall, relevant regulations, recall strategy and communication, and the responsibilities of the firm and the FDA throughout the process.

Recalls should occur when a medical device is determined to be defective and when it could be a risk to health. They involve a removal or correction of a marketed product that's in violation of the Federal Food, Drug, and Cosmetic Act.

A recall is a voluntary action that can be taken at any time by a firm to protect the public health and well-being from products that present a risk of injury or a gross deception or are otherwise defective.

A recall is an alternative to an FDA-initiated court action for removing or correcting violative products through seizure or import detention. Legally, the FDA can require a firm to recall a device that's associated with significant health problems or death, if the firm refuses to do so. This is a rare occurrence.

Here are a few definitions for recalls. A violative product does not meet the applicable regulatory and statutory laws within the scope of a recall. Typically, medical device recalls occur because the device is either misbranded or adulterated.

A device is considered misbranded if its labeling is false and misleading; its labeling is incomplete, for example, the device name is incorrect or contraindications are missing; its labeling does not have adequate directions for use, or it's sold or distributed for uses in violation of cleared indications or device regulations.

A device is considered adulterated if it's subject to a performance standard and does not comply with all the requirements of the standard; it's a Class III device and fails to conform to the requirements for an approved PMA or a notice of completion of a product development protocol; it's a banned device; it's in violation of good manufacturing practice requirements or it fails to comply with an IDE.

FDA classifies recalls according to the relative degree of health hazard presented by the product.

For a Class I recall, there is a reasonable probability that the use of or exposure to a violative product will cause serious adverse health consequences or death. We define a serious adverse health consequence as any significant adverse experience including those that may be either life-threatening or involve permanent or long-term injuries, but excluding injuries that are non-life threatening and that are temporary and reasonably reversible.

A Class II recall is the most common classification for orthopedic devices. In these cases, exposure to or use of the product may cause temporary or medically reversible adverse health consequences or the probability of a serious adverse health consequence is remote.

Finally, a Class III recall is not likely to cause adverse health consequences.

There are several ways FDA can become aware of a recall. Most commonly, an 806 report is voluntarily submitted by a firm. FDA may also become aware of a recall through FDA inspections, including:

- Directed or routine inspections; allegations such as consumer or trade complaints;
- Adverse event reports like MedWatch, MedSun, or MDRs;
- OHT reviews;
- Mutual recognition agreements with foreign regulatory authorities;
- Information received by a firm, repackager, or distributor, and from competitors.

Once the firm has determined that the reason for their action is to reduce a health risk or remedy a violation, the report must be submitted to FDA within 10 working days from the time the firm initiates the correction or removal. The firm should submit to their division recall coordinator or DRC. When there is a not a risk to health involved, a report to FDA is not required, but the firm must keep a record of the correction or removal.

There are several cases in which firms are exempt from reporting. These include cases where an action is taken to improve performance or quality that does not reduce risk or mitigate a failure or noncompliance; a correction or removal that is part of regularly scheduled preventative maintenance, including the replacement of parts at the end of their normal life expectancy and repairs of an unexpected nature.

Another exemption includes a market withdrawal involving a minor violation that would not be submitted to legal action by the FDA or involving no violation, for example, normal stock rotation practices or obsolescence. Stock recovery of devices is also exempt when the device has not been marketed or has not left the direct control of the manufacturer.

Finally, safety alerts are also exempt from reporting. A safety alert is a notification that the use of the device may, in certain circumstances, pose a risk of substantial harm from situations such as misuse, failure to follow labeling directions, or connection to other devices.

When a firm is reluctant to recall, FDA may take several actions, including:

- A discussion of our evaluation of risk with the firm;
- Public notification;
- A mandatory recall;
- Seizing the product;
- Injunctions;
- Placing the firm on import alert; and
- Foreign country notification.

This slide presents some regulations that are relevant to recalls. Twenty-one C.F.R. 7, Enforcement Policy, provides guidance for firms to conduct an effective recall. This regulation sets forth specific recall procedures for FDA to monitor recalls and assess the adequacy of the firm's effort.

Twenty-one C.F.R. 806, Medical Device Reports of Corrections and Removals, describes the reporting requirements for any correction or removal of a medical device as a part of a recall.

Finally, 21 C.F.R. 810, Medical Device Recall Authority, describes the procedures the FDA will follow in exercising its recall authority. In rare situations where the manufacturer or importer fails to voluntarily recall a device that poses a risk to health, FDA may issue a recall order to the manufacturer under 21 C.F.R. 810.

Let's take a closer look at the information described in 21 C.F.R. 806, starting with some definitions. A correction involves the repair, modification, adjustment, relabeling,

destruction or inspection of a device without its physical removal from its point of use to some other location. This includes further patient monitoring or monitoring for specific signs and symptoms.

A removal involves similar actions such as a repair or modification of the device; however, the device is physically removed from its point of use to some other location.

Under 21 C.F.R. 806, a risk to health can mean two things. The first option is there is a reasonable probability that the use of or exposure to the product will cause serious health consequences or death. The second option is that the use of or exposure to the product may cause temporary or medically reversible adverse health consequences or an outcome where the probability of serious adverse health consequences is remote.

Under 21 C.F.R. 806, there are several mandatory items that must be reported.

These include:

- The report number using FAI or registration number;
- The name, address and telephone number of the manufacturer or importer. We recommend including e-mail addresses as, well.
- Device identification including the brand name and the common name, classification name or usual name of the device and the intended use of the device;
- The marketing status and associated premarket device numbers or a device listing number;
- The model, catalog or code number of the device and the manufacturing lot or serial number of the device or other relevant identification;
- A description of the events and the corrective or removal actions that have been and are expected to be taken;
- Information about illness or injuries associated with device use and any related

MDRs;

- The total number of devices manufactured and distributed and the number per batch or lot.
- You should also specify if any were implanted.
- The date of manufacture or distribution and the device's expiration date or expected life;
- The names, addresses and telephone numbers of all domestic and foreign consignees, and the dates and number of devices distributed to each such consignee;
- A copy of all communications regarding the correction or removal; and finally
- If any required information is not immediately available, a statement as to why it's not available and when it will be submitted.

During a recall, a firm's responsibilities are to

- Determine the need for a recall and scope;
- Conduct a risk assessment and root cause analysis;
- Submit a report of correction or removal, also known as an 806 package;
- Execute appropriate recall actions and strategy. This includes developing corrective and preventative actions to fix the problem and prevent future occurrence;
- Notifying all consignees;
- Developing a plan for destruction or reconditioning and conducting effectiveness checks.

The firm should also provide status reports to FDA, improve product quality for the future, and require termination of the recall when they have completed their activities and heard from their consignees.

Let's dive deeper into the recall strategy. A recall strategy is a planned course of action that addresses the depth of the recall, the need for public warnings, and the extent of effectiveness checks for the recall. Please note that effectiveness checks are something you do to document that the appropriate person received the notice and acted appropriately.

The recalling firm should develop a strategy that considers the following factors:

- Results of a health hazard evaluation used in identifying the product;
- The degree to which the product's deficiency is obvious to the consumer or user;
- The degree to which the products remain unused in the marketplace; and
- Continued availability of essential products.

The FDA will review the adequacy of a proposed recall strategy and recommend changes as appropriate; however, the firm should not delay initiation of a recall pending review of its recall strategy.

Here's more information on what to include when notifying consignees. You should include the correct title that clearly states the notification is for a recall. The notification letter should fully identify the product in their possession that is the subject of the recall. You should describe the reason for the recall and the risks to health, preferably within the first paragraph. You should also indicate that further distribution or use should cease immediately. Direct accounts should notify customers who receive the product where appropriate. The letter should also include instructions on what to do with the product. Finally, it's helpful to remind customers to submit medical device reports, or MDRs, to FDA and to provide a link to the MDR submission portal.

Please note that the notification letter should not contain irrelevant qualifications, promotional materials, or any other statement that might detract from the message.

During a recall, FDA has several responsibilities. This chart shows an overview of how FDA and industry work together during a recall. The Office of Regulatory Affairs, or ORA, serves as a liaison to industry and plays a key role in developing the 806 package. Once ORA is notified of a recall, they review the 806 package, gather additional information, provide a recommendation, conduct audit checks, review status reports, and terminate Class II and Class III recalls.

The Center for Devices and Radiological Health, or CDRH, has several responsibilities during a recall. These include evaluating risk to classify the recall, evaluating the strategy, and determining the effectiveness and audit check levels. They also conduct shortage assessments as warranted, determine if press is needed, and identify additional follow-up actions or concerns.

Here's a closer look at the role of CDRH during a recall. When ORA provides the 806 package to CDRH, the recall is assigned to a lead reviewer to coordinate the clinical and technical review process. CDRH determines whether the 806 package is adequate or if additional information is needed from the firm.

The reviewer must work promptly with the medical officer to classify the recall. Typically, this is accomplished by identifying a comparable recall as a precedent or using a policy to directly classify the recall based on sufficient historical precedent. If those two options are not possible, a health hazard evaluation, or HHE, is needed to classify the recall. CDRH must quickly determine if the recall is Class I, which poses the greatest risk to public health. Otherwise, the process for a Class II or III recall is followed.

In addition to classifying the recall, CDRH reviews the firm's recall strategy and communication. The recall classification recommendations and results of the review are communicated back to ORA, who continues to work with the firm to close the recall. Throughout the review, OHT 6 collaborates with the firm, ORA, and the Recalls and

Shortages Teams in the Office of Regulatory Programs in CDRH, to keep them in the loop regarding any communication on the recall. CDRH is working to streamline the recall review process to ensure that its classification is communicated to the public promptly following receipt of recall information.

A recall will be terminated when FDA determines that all reasonable efforts have been made to remove or correct the product in accordance with the recall strategy. A recall is terminated when it is reasonable to assume that the product has been removed and proper disposition or correction has been made commensurate with the degree of hazard of the recalled product.

A firm may request termination of its recall by submitting a written request to its DRC stating that the recall is effective and by providing the most recent recall status report and a description of the disposition of the recalled product. Written notification that a recall is terminating will be issued by its DRC to the recalling firm.

This slide shows some of the places on fda.gov that recalls are posted and can be searched.

This slide lists several resources for recalls, including the relevant regulations, general information on FDA's website, and several guidance documents.

In conclusion, we recommend following the requirements in 21 C.F.R. 806 and reporting in a timely manner. Submitting adequate and accurate information will help FDA classify the recall risk and evaluate the recall strategy and communication. This will require continued collaboration between firms and FDA to ensure that all appropriate steps are taken to mitigate risk to patients.

Thank you, and this concludes my presentation.

MR. SPEER: Thank you, Dr. Cristino.

I want to remind you all, if you have questions and comments throughout, you can

submit those to an e-mail address. Let me read that e-mail address for you. It is oht6-feedback@fda.hhs.gov. Again that's oht6-feedback@fda.hhs.gov.

Let's move on to our next presenter -- presenters, excuse me, and the topic is recalls best practices, and this will be presented by Jay Kadakia and Joseph Russell, both Jay and Joseph are with FDA. Let me give some introductions for both of our presenters.

Jay Kadakia has been serving as lead reviewer in the Division of Joint Arthroplasty Devices, Hip Arthroplasty Devices Team, within the Office of Health Technology 6, the Office of Orthopedic Devices at FDA since 2018. He received his master's in biomedical engineering from Perdue University, and bachelor's in biomedical engineering from Rutgers University. Mr. Kadakia is a biomedical engineer with experience in reviewing various joint arthroplasty devices, with specialized experience in additive manufacturing and magnetic resonance compatibility reviews. Mr. Kadakia has experience in both premarket and postmarket compliance submissions including reviewing recalls, medical device reports, established inspection reports, and allegations. Mr. Kadakia received various awards related to premarket and postmarket reviews at the office and center level.

Our other presenter is Joseph Russell. Joseph Russell has been serving as a lead reviewer in the Division of Joint Arthroplasty Devices, Shoulder Arthroplasty Devices Team within the Office of Health Technology 6, Office of Orthopedic Devices at FDA since 2020. He received both his master's and bachelor's in bioengineering from the University of Maryland in College Park. Mr. Russell is a general engineer with experience in reviewing various joint arthroplasty devices, with experience in mechanical testing. Mr. Russell routinely reviews both premarket and postmarket compliance submissions, including recalls. Mr. Russell has prior industry involvement in mechanical design, design controls, and risk management activities.

MR. KADAKIA: Good morning, my name is Jay Kadakia and I am a lead reviewer in

the Hip Arthroplasty Devices Team in the Division of Joint Arthroplasty Devices in OHT 6. I am presenting today with Joseph Russell, a leader reviewer in the Shoulder Arthroplasty Devices Team. We appreciate the opportunity to share with you tips and recommendations for best practices when conducting a recall. Please note, these are not an all-inclusive list.

In this slide I will recap the firm's responsibilities when it comes to recalls. Firms should investigate root cause and identify the scope to ensure all affected products are recalled and avoid the need to initiate another recall for the same issue. In OHT 6 we have referred to this as one-and-done approach.

Firms should develop the right strategy to ensure the actions make sense and prevent the affected products from reaching patients.

Firms should develop appropriate CAPAs, or corrective actions, to address root cause and minimize the same issue from reoccurring. This is also important in ensuring the corrective actions are effective in correcting the problem and do not lead to new unexpected failures or new risks.

Firms should communicate to all consignees, for example, hospitals and distribution centers, that have received the affected products and provide adequate instructions and communication of risks and potential harm of the device to ensure proper actions are taken to mitigate any potential risks.

Firms should develop a plan for what to do with a device once it is returned for appropriate disposition of affected products.

Firms should conduct checks to ensure the strategy is effective.

Please submit the 806 report to the Office of Regulatory Affairs Medical Device Division to notify the Agency of the correction or removal. The report can be sent via e-mail or by using the e-submitter. After the notification, continue to provide status reports to the Agency. And once all responsibilities are complete, be sure to request a recall termination.

In the rest of this presentation we will cover some, but not all, of these points in more detail to provide recommendations and best practices in reporting, and share examples of where inadequacies have been observed by OHT 6. The intent is to share these best practices to help improve the overall quality of devices.

First, we will discuss scope, as it can drive the strategy and the rest of the recall process. Scope determination is essential to ensure all affected products are identified and proper actions are taken to prevent any adverse events to patients.

In the 806 report, it is recommended to provide adequate information to describe how the problem was discovered and how the firm has investigated the issue to determine the correct scope. For example, it is expected that the firm will do a systemic review of complaints or device history records, depending on potential root cause, to determine the appropriate scope. Based on the investigation, be sure to clearly state that the recall was limited to a specific lot or a period of manufacturing, etc.

Scope should not be limited to those products with verified complaints. You need to think big picture and potential impact to other products or lots and remember the one-and-done approach. It is very important to avoid multiple recalls for the same issue because the longer the affected products remain in the field, the higher the likelihood of adverse events and patient harm. Next, I'll provide an example of reports submitted with an inadequate scope.

We received a recall for an arthroplasty device for debris observed in device packaging. There is potential for debris on the device to be implanted causing inflammation and other body reactions that could affect the success of surgery. Based on complaints received, the firm determined that this issue only impacted one product design and other products with similar packaging was not included in the initial scope. After some time, complaints were received for other designs with similar packaging, which led to other

subsequent recalls. This presents a concern since products outside of the initial scope may continue to be used and delaying the action presenting risks to patients. Remember to think big picture, take systemic actions and revise CAPA as needed. If after submitting an initial recall you determine that the same correction or removal should be extended to other lots or batches of the same device, please initiate the extension by amending the report via an amendment to original report number within 10 working business days, and notify the ORA Medical Device Division as soon as possible.

I will now discuss expectations on recall strategy. When determining recall strategy, consider the depth of distribution chain, alerting the public of potential harm, ensure all consignees have been notified and are taking adequate steps to mitigate the risks, and ensure correction or removal of affected products. Lastly, describe and specify the methods for the checks and the level of effectiveness of your recall strategy.

When a firm is considering the right course of action, please consider the following: Results of the risk assessment; how easy it is to identify the affected products; is it one component of a hip system; are the various bone screws compatible with multiple systems such as plates, external fixators, spinal rods, etc.; how obvious is the issue to the end user; how difficult is it for the user to recognize the affected product. Please ensure this is addressed in the communications to consignees. The strategy also needs to take into consideration other products available to patients and whether removal would cause a potential shortage. If there are multiple steps such as a workaround before a new design can be implemented, plan for each step.

A situation where an 806 report submitted early without time to plan recall strategy is shown here. We received a recall with a unique bone screw with a device-specific driver to assist with implantation. The issue involved the inability for the driver to mate with the screw head. This is concerning as it can result in delay in surgery with the surgeon having to

figure out how to implant the device. The firm wanted to ensure that an 806 report was submitted to the Agency early in the recall process and therefore determined the best course of action was to remove drivers from the field. However, this recall strategy and communication to users did not address the question of what users would do to implant bone screws without the corresponding driver. In addition, it was not clear how and when the firm would correct the issue with the driver, for example, investigate changing the design of the device to replace the product in the field. This led to additional questions and confusion in the field.

We recommend that the firm reach out to the ORA Medical Device Division, involve the Agency before submitting recalls during instances when the strategy is difficult to plan. After the 806 is submitted, we recommend that the firm maintain constant communication and provide updates on the progress.

Please note that there is a time lapse between when OHT 6 receives the classification assignment and when the recall package is submitted. We encourage firms to update any information such as scope and recovered devices early and periodically to help reduce FDA time to classification. This information is an important consideration for a classification decision as changes can impact probability of risk. Overall, we recommend the firm to provide CAPA numbers and methods with details in the 806.

In terms of reporting the corrective actions, we recommend firms provide relevant information on the planned corrective actions. Please include initial root cause. If one cannot be identified at the time of reporting, please describe potential root causes with the corresponding planned corrective action. In the 806 report, please summarize the immediate actions taken to mitigate the risks to patients. Summarize any long-term planned and systemic corrective actions to prevent reoccurrence of the issue.

Please note that not all corrective actions are required to be completed by the time

of recall notification to FDA, but it is recommended to include as much information as possible. This way, the Agency can work with the firm if there is a need for improving the actions proposed to ensure the actions are adequate. Generally indicating CAPA is under investigation without additional information makes it difficult for the Agency to understand the actions a firm is thinking about taking. It is also recommended, if possible, to include the CAPA as part of the 806 package.

Please note that not every situation would require a new CAPA, unless it's required by the firm's procedure. It is important that firms investigate repeated recall events, as they provide important measures in respect to the initial corrective actions. It is important to develop a robust CAPA plan and even more so, a robust CAPA system to prevent reoccurring quality issues.

If information is requested by the FDA and it is not immediately available, please issue a statement as soon as possible detailing why the information is not available, a planned approach for obtaining the information, and an estimated time frame for when the information will be available to the FDA.

Here is an example of a recall we received, which is related to an orthopedic instrument or a modular connection between the handle and impactor with disassembling and falling apart during use. The firm had stated in the 806 report that they are planning on changing the instructions on the labeling; however, this may not be sufficient to prevent reoccurrence and concluding user error may not be sufficient.

As mentioned earlier, it is recommended to provide the list of potential causes and communicate with the FDA, especially if firms are unclear on what's an appropriate corrective action. Ensure that you consider immediate and long-term corrective actions. Long-term corrective options may involve quality system changes such as training, updates to procedures, and making design changes to the device. For this situation, a design change

may be more appropriate. At the very least, the FDA will want to know if a design change approach was explored by the firm and how it was determined that there is no need for a design change. Remember to continuously provide updates related to CAPAs.

I will now pass it to Joseph Russell for the remaining topics on the recalls best practices, starting with a discussion on design changes.

MR. RUSSELL: Thanks, Jay. Good morning, everyone, my name is Joe Russell. I'm a lead reviewer in the Shoulder Arthroplasty Devices Team. As Jay just stated, we would like to briefly discuss design changes, as we have seen various recall CAPAs that have resulted in changes to a recalled device.

One such scenario may be where a 510(k) is submitted for design changes, noting some complaints or issues in the field, but with no recall submitted. You may consider both the regulation and the risk-based analysis to determine whether recalling the previous device was appropriate.

Another scenario may be a recall where a proposed long-term CAPA is a design change with no discussion about whether submitting a 510(k) is necessary. Please review the FDA guidance issued on October 25th, 2017, titled "Deciding When to Submit a 510(k) for a Change to an Existing Device." Design changes could encompass modifications such as minor manufacturing or dimensional changes. I would like to stress that open communication is key. If you are unsure if a recall or a new 510(k) is necessary due to a design change, FDA welcomes discussion surrounding the appropriate regulatory approach.

Moving on to some best practices for communicating with end users and the FDA. Your 806 report to FDA should include a list of consignees. The table here displays a list of various situations for consignees, such as who was notified, did they respond and inform you of quantities of products on hand or did they not respond.

In communication with consignees, we recommend both electronic and written

communication as a first step with multiple attempts at calling the consignees as a follow-up to those that did not respond. It is important to indicate in the 806 report which consignees have not been communicated to and to have a follow-up plan to address those that have not responded.

Note, you are expected to submit status reports to your district recall coordinator monthly on how many consignees have responded to your notification, how many products have been returned, etc.

After communication to consignees, it is important to understand and report the quantity of products in the field. The 806 and status reports should provide specific numbers on the products returned or corrected by the consignee, the number of effectiveness checks, and the results. Please include an estimated time frame for completion and keep the FDA updated for any potential changes. Ensure the manufacturing date and time frame for distribution of products is adequately documented in the 806 report. Eight-oh-six requires that you provide both consignees within and outside the U.S.; however, please separate the U.S. consignees from those outside the U.S.

After obtaining the quantity of products, you may be considering a plan for controlled complete destruction or reconditioning of the product. For both processes, please have procedures in place to separate products that are being deconstructed or reconditioned from the ready-to-ship products that are not part of the recall. An example of marking products for destruction would be to create scratch marks, lines or large X's on components.

For reconditioning, the FDA has information about the process on our website. As part of the reconditioning process, please note that you should provide a justification demonstrating that reconditioning will not affect the safety and effectiveness of the device. If you have trouble justifying product reconditioning, we recommend that you communicate

with the FDA and consider a controlled destruction. An example of reconditioning could involve recalls related to labeling concerns where the product is recalled and a new label is applied. This may be an appropriate approach for reconditioning. However, if a product is provided sterile and it is recalled due to a broken sterile barrier, please note that there may be potential concerns with the resterilization of the product as a corrective action.

After submitting an 806 report and throughout the recall process, please provide status update reports to the district office. Any questions about the reports should be directed to the specific district office. We want to emphasize that these reports are important in providing updates to CAPAs and other ongoing activities related to the recall.

If there is missing information in the 806 report, please note that the regulations state that a statement to the FDA should be provided. FDA takes recalls very seriously and will maintain constant communication with the firms continuously submitting incomplete information. If issues cannot be resolved, the FDA may take regulatory actions, such as inspections, that could result in a warning or untitled letters or may pursue civil money penalties. FDA prefers to collaborate and work together with firms to resolve issues well before there is a need to pursue additional regulatory action.

In addition, we want to remind you about the quality system requirements seen in 21 C.F.R. 820. The regulations include establishing and maintaining procedures for implementing CAPAs. Systematic approaches assist with ensuring the necessary corrective fixes are made on all units. Good implementation of quality systems support the recall process to make sure CAPAs are successful.

To conclude, the recall process requires various steps to be taken by the firm. We recommend communicating and working with the FDA to resolve these issues together. Systematic approaches should be considered for all recall issues, along with both short-term and long-term solutions.

At FDA, our mission is to protect and promote public health. It takes all of us to continue to support this mission by having constant communication and a robust recall process to ensure devices remain safe for our patients.

Finally, please note this guidance for industry issued in March 2020 regarding product recalls. This guidance contains a checklist of documentation and relevant information to provide to the FDA during recall processes.

With this, I will pass the presentation over to Teresa to discuss recent recall trends and analysis. Thank you for your time and attention this morning.

MR. SPEER: Thank you, Jay and Joe. And before we hand things over to Teresa, let me remind you that if you have questions throughout, to submit those via e-mail to oht6-feedback@fda.hhs.gov.

Now let's move on to Teresa's presentation on recalls analysis and trends. Teresa Palacios-Hernandez is with FDA and she's a senior staff fellow/lead reviewer/biologist since 2019 in the Division of Joint Arthroplasty Devices, Knee Arthroplasty Devices Team, DHT 6A1, at the Office of Health Technology 6, Office of Product Evaluation and Quality, Center for Devices and Radiological Health, U.S. FDA, performing TPLC evaluation of orthopedic devices, recalls, allegations, premarket submissions and pre-emergency use authorizations for COVID-19 pandemic.

Additionally, she serves as a subject matter expert in the field of biocompatibility with focuses in nanotoxicology, general biocompatibility, and toxicological risk assessment and sterility. Dr. Palacios worked previously as a postdoctoral fellow in the Division of Biology, Chemistry, and Material Sciences at CDRH/FDA and the Department of Material Science and Engineering at Johns Hopkins University and in the Department of Food and Chemical Engineering at the Universidad de Las Américas Puebla, Mexico. She also was assistant professor of UPAEP University in Mexico where she coordinated different research

projects in nanomedicine.

DR. PALACIOS-HERNANDEZ: Good morning, everyone. My name is Teresa Palacios-Hernandez, a lead reviewer within the knee team of the Division of Joint Arthroplasty Devices within OHT 6, Office of Orthopedic Devices. I will discuss today about the recall analysis and trends in orthopedic devices that was performed by the Agency.

During my talk, I will provide a background for the analyses performed to the recalls received by FDA related to orthopedic devices, and I will identify the top devices recalled, the main root causes for orthopedic recalls. I will present the top products recalled and then main causes associated with the recalls, and I will finally present the conclusions for these analyses as well as general recommendations on behalf of the Agency, in order to decrease the number of recalls needed.

I will start this presentation mentioning that since 2018-2020 to date, 452 recalls have been received by FDA related to orthopedic devices with multiple root causes associated, then an analysis for other recalls received during this period as well as the associated root causes was performed.

The results that the Agency obtained indicated different trends in the number of recalls received by the Agency that were associated with a specific probable cause and also was noted that there are common root cause issues associated with these products. Therefore, FDA is providing the results from these analyses for industry awareness of the main problems associated with recalls, the main product codes affected, and general recommendations to reduce the number of recalls in orthopedic devices.

After reviewing the 452 recalls received by the FDA that were associated with orthopedic devices since 2018-2020 to date, it was that there remained two recalls were identified as Class I, 444 recalls were identified as Class II, and seven recalls were classified as Class III. For orthopedic devices, it has been observed in general terms that the most

common recalls submitted to the Agency have been identified as Class II.

For the total number of recalls received by the Agency and associated with orthopedic devices, we determined that the top five orthopedic product codes that were recalled for period of 2018-2020 to date were knee prostheses in cemented version as top one with product code JWH; orthopedic manual surgical instruments with pro code LXH as top two; orthopedic stereotaxic instruments with pro code OLO and fixation plates with pro code HRS with equal number of recalls as top three in the analysis; fixation drugs with product code HSB as top four; and hip prostheses in uncemented version with product code LPH were identified as top five in this analysis.

Additionally, the main root causes associated to the total number of recalls received by the Agency were identified as follows: process control was identified as top one root cause, followed by device design in number two, and different pathogen issues were identified as top three in the analysis. Also, nonconforming material or component and employee errors were found as top four. And finally, the recalls with root causes under investigation by the firm were found as top five in our analysis.

We analyzed on a year-by-year basis the top three product codes recalled for period 2018-2020 to date, and it was observed that the overall number of recalls associated with knee prostheses with pro code JWH and manual surgical instruments with product code LXH has decreased. In 2018, the Agency received 38 recalls, in 2019 we received 22 recalls, and for 2020 to date only 19 recalls were received. However, for the stereotaxic instruments with product code OLO, the trend obtained shows an increase in the number of recalls received, since in 2018 and 2019 six recalls were received by the FDA for each year and in 2020 to date, 13 recalls were submitted to the Agency by industry.

Additionally, for the top three product codes recalled in period 2018-2020 to date, the top four root causes were identified. In general terms, the most common root causes

associated with these pro codes for the period evaluated were process control, nonconforming material or component, device design, and packaging issues. Additionally, it was noted that the determination of the root cause is still ongoing for most of the recalls received for the product code OLO.

At the conclusion from a recall analysis, it is important to consider that recalls that come to the Agency have been related to different causes such as different problems that may appear during the design of the devices, problems related to material suppliers or to the existing acceptance activities associated with manufacturing defects.

FDA has communicated some of these findings to industry in different public meetings such as OSMA, in order to make industry aware of such issues and to offer a collaboration in order to assist industry to decrease their number of recalls.

In general terms, it is important to consider that evaluating process points such as initial device design considerations, the given process validations, the improvement of device inspections, the generation of additional acceptance activities for labeling or product change, and additional improvements in controlling incoming materials, components, or suppliers may greatly contribute to improve the process is effective and therefore decrease the number of recalls generated.

To conclude this talk, we recommend that manufacturers conduct internal analyses to identify their points of improvement and take the necessary actions to reduce the number of recalls.

Finally, I would like to thank the recall team for their participation in elaborating these 2018-2020 recall analyses. And this concludes my participation. Thank you very much for your attention.

MR. SPEER: Okay. Thank you, Dr. Palacios.

And again, I want to remind you all, if you have questions and comments, I'm going

to give you that e-mail address yet again, it's oht6-feedback@fda.hhs.gov.

Now we're going to have our first Menti survey for today and this will be presented by Sahlee Sabala with FDA. Sahlee Sabala is a regulatory health project manager in the Office of Health Technology 6, Office of Orthopedic Devices at FDA Center for Devices and Radiological Health. She has over 10 years of public health experience in both local and international settings and developed strategies in enhancing program operations with a strong emphasis on health interventions and preventions to improve quality of life through collaboration with multicenter -- or multicultural, excuse me, environment.

She joined FDA in 2016 and worked as a project manager in the Center for Tobacco Products and served as a contracting officer's representative managing multimillion dollar tobacco research contracts. In 2018 she joined CDRH as project manager and developed process improvement in managing sponsors meeting requests and led the first strategic planning for fiscal year 2020. She earned her master of public health from Kaplan University in 2014 with honors.

Sahlee.

MS. SABALA: So good morning, everyone, and thank you, Jon, for that wonderful introduction.

So for today's first Menti survey, I would like to remind everyone that there are two ways to participate in this survey. First, use your smartphone device, you can scan the QR code located on the screen or you can go to menti.com and enter the seven-digit code to get into the Menti questions. So let's get on to our first question about recalls.

So the first question is: In one or two words describe what you think when you hear the word recall. And there is no right or wrong answer to this. Feel free to put in your answers and because we are having this workshop live, there are some few seconds delay in getting your answers into the system, so just bear with us and we will give people time to

get their answers populated into the system. So while we're waiting about, I just want to keep reminding folks that we love to hear feedback comments to us, and feel free to enter those to oht6-feedback@fda.hhs.gov and that e-mail information will be on the screen for your reference. Let's give folks a couple more seconds to get their answers into the survey. And I believe there's about 20, 30 seconds lag to get all the answers into the system.

(Pause.)

MS. SABALA: Okay, wonderful. I see a lot of questions are being populated on the screen. Wonderful, thank you for your participation. Okay, great. So I guess I'll move on to the next question.

Okay, the second question: What are some tools (e.g. forms, guidance document template, etc.) you would like to see FDA develop to help you with the recall process? Again, there's no right or wrong answer, those are just examples of whatever comes into your mind --

(Audio interference.)

MS. SABALA: -- what your comments are. And for those who are just calling in, you can go to menti.com and enter the seven-digit code to get into these questions -- can use the QR code to get you into the survey questions, as well. I'm seeing answers populating on the screen. Let's give folks a couple more seconds to get more comments from the audience.

(Pause.)

MS. SABALA: Wonderful. Okay, I guess we can move on to the next question. The next question is: Briefly, what is the process for assessing risk to identify and triage problems or issues, like health hazard evaluation or health risk assessment?

And I just want to read through it one more time and we'd like to hear your comments and feedback or any questions you might have for us. You can send those via

e-mail at oht6-feedback@fda.hhs.com and you will find that e-mail address on the screen or the reference. And of course, we are having this workshop live and there's also a few seconds delay in getting all of the answers into the website, so please bear with us. Slowly but surely, I can see that people have been responding and the questions are being populated on the screen. Thank you for your participation today. I guess we can give a couple more seconds for people to put in their responses.

(Pause.)

MS. SABALA: Oh, wow, we're getting really good feedback and this is really important to us. Okay. I guess with that, we can move to the next question.

All right, next question: How many percent of the time do you have a root cause determined before versus after submitting 806 report? It could be 0 to 25, 25 to 50%, 50 to 75% or 75 to 100%. There is no right or wrong answer. We would love to get your answers or comments on this. And if you have further questions specific to this workshop, you may send it over to the e-mail address on oht6-feedback@fda.hhs.gov, which can also be found on the screen for your reference. Wonderful answers, thank you all for your participation.

Do we have another question? Yes. Next question: What is the most common root cause at your facility? Again, there's no right or wrong answer and we would love to see or hear what your facility has for your root cause. Okay. I believe this is the last question for this -- let's give a couple more seconds to take a time lag. All right.

(Pause.)

MS. SABALA: Okay. Well, thank you all for your participation and I'll turn this over to Jon.

MR. SPEER: Thank you, Sahlee.

Again, the e-mail address if you have questions or comments, I know I'm sounding like a broken record on this, but bear with me, I just want to make sure you all have the way

or the means to be able to provide that feedback, but the e-mail address again is oht6-feedback@fda.hhs.gov. I think we've got a little bit of background noise, so bear with me a second.

But anyway, let's move on to our next presenter and presentation. The next topic will be MDRs overview and requirements, and this will be presented by Carole Wolfe. Carole Wolfe is with the FDA and she's a lead reviewer and biomedical engineer in the Shoulder Arthroplasty Devices Team in the Division of Joint Arthroplasty Devices. Ms. Wolfe received her master's degree in applied biomedical engineering from Johns Hopkins University and has over 5 years of quality systems experience.

MS. WOLFE: Good morning, my name is Carole Wolfe and I am a biomedical engineer and MDR reviewer in the Division of Joint Arthroplasty Devices within OHT 6 Office of Orthopedic Devices. Today I will be providing a brief overview of the FDA's Medical Device Reporting or MDR system and requirements.

Twenty-one C.F.R. Part 803 establishes the requirements for medical device reporting for device user facilities, manufacturers, importers, and distributors. MDRs allow for both FDA and manufacturers to identify and monitor adverse events and certain device malfunctions, as well as facilitate the correction of these problems in a timely manner. MDR reports also help to protect the public health by helping to ensure that devices are not adulterated or misbranded and are safe and effective for their intended use. FDA currently receives more than two million MDRs per year relating to device malfunctions, serious injuries, and deaths that may be associated with devices.

Twenty-one C.F.R. Part 803.3 Section (o) defines a reportable event as an event that user facilities become aware of that reasonably suggests that a device has or may have caused or contributed to a death or serious injury. A reportable event is also defined as an event that manufacturers or importers become aware of that reasonably suggests that one

of their marketed devices may have caused or contributed to a death or a serious injury or has malfunctioned, and that the device or similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur. FDA assumes that once a device malfunction has occurred, it will recur.

In the next few slides I will briefly define what is meant by the phrases "caused or contributed," "serious injury" and "malfunction."

In relation to MDRs, the phrase "caused or contributed" is defined as a death or serious injury that was or may have been attributed to a medical device or a medical device may have been a factor in a death or serious injury which could lead you to device failure or malfunction, improper or inadequate design, problems with the manufacturing or labeling of the device or use error from the patient and/or surgeon.

The phrase "serious injury" is defined as an injury or illness that is either life-threatening, results in permanent impairment or damage to a body function or structure, or requires medical or surgical intervention to preclude permanent impairment or damage to a body function or structure.

Finally, a malfunction is defined as the failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of the device refers to the intended use for which the device is labeled or marketed, as defined in 21 C.F.R. 801.4. For a malfunction to be reportable, it must be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

I now want to briefly touch on the mandatory reporting time frame guidelines for MDRs. Time frames are organized by the reporting body (manufacturers, importers, or user facilities) and the event type, mainly death, serious injuries, and malfunctions. There are

also requirements about to whom you must report, whether it's FDA, the manufacturer, or both. Finally, there are specific time frames in which the events must be reported, ranging from five business days after becoming aware of the event, to 30 calendar days after becoming aware of the event.

When submitting an MDR, there are three types of MDR submissions that can be chosen. Individual or initial reports are submitted when the reporting body has initially become aware of the adverse event that is MDR reportable.

Supplemental or follow-up reports are submitted for individual MDRs when additional information relating to the initial MDR has been obtained. For example, this may include new information regarding the adverse event investigation.

Finally, voluntary malfunction summary reports, or VMSR, can be submitted quarterly by manufacturers. I will now go into a bit more detail about the VMSR program and what it entails.

In August of 2018, FDA published a *Federal Register* notice that outlined the framework for the VMSR program, which is an alternative reporting requirement granted under 21 C.F.R. Part 803.19. VMSR allows for bundling multiple events sharing the same malfunction or combination of malfunctions into a summary format in a single MDR which is submitted quarterly.

The VMSR program does not allow for manufacturers to report death or serious injuries in a summary format, and participation in the program does not change the manufacturer requirement to investigate malfunction events.

Only devices and eligible product codes that have been in existence for more than 2 years may be reported using this format. Currently, 238 out of the 251 orthopedic product codes are eligible for VMSR. Of note, the program includes Class I, Class II, and Class III devices. The eligibility status of product codes can be found in the product classification

database on FDA's website. Requests to add product codes to the program may be submitted to the MDR team within the Office of Regulatory Programs at the e-mail provided.

Although the VMSR program includes device malfunctions reported by manufacturers, there are some situations where a device manufacturer or a malfunction is not eligible. Reportable malfunctions associated with 5-day reports or are subjects of certain device recalls are not eligible.

If a device is the subject of a recall to address a malfunction, any reportable malfunction of the same nature that involves the same or similar device marketed by the manufacturer must be submitted as an individual report until the recall is terminated. New types of malfunctions that have not previously been reported are also not eligible.

FDA may determine that a public health issue requires an individual or initial report and thus is not eligible for a VMSR. Additionally, FDA may determine that a specific manufacturer cannot participate in the program.

Since the program's inception in August 2018 through March 2020, 38 establishments across 27 firms have participated in the program. The summary reports submitted represent 134 devices or product codes with more than 5100 reports that are summarizing nearly 63,000 malfunction events. Considering that most of the orthopedic product codes are eligible for the VMSR program, participation in the program is worth thinking about for orthopedic device manufacturers.

Now that I have reviewed what constitutes an MDR reportable event, the reporting time frames, and the types of MDR submissions, I will explain what is not an MDR. MDRs are not complaints. As described in 21 C.F.R. 820.198, a complaint is a written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for

distribution. Although they are not MDRs, complaints are reviewed, evaluated, and documented by FDA for possible MDR reportability. Finally, it is important to note that the volume of MDRs does not equal the complaint rate relating to a device.

In addition to submitting reportable adverse events to FDA, there are other regulatory requirements that must be met regarding MDRs. The device manufacturer must conduct a complete investigation of each adverse event. User facilities, importers, and manufacturers must develop, maintain and implement written MDR procedures for internal systems and documentation and recordkeeping requirements.

Additionally, user facilities, importers, and manufacturers must establish and maintain MDR event files or records. Specific requirements for user facilities, importers, and manufacturers can be found in 21 C.F.R. Section 803, Subparts C, D, and E respectively.

Finally, AI letters may be sent by FDA to the manufacturer to collect additional information or to clarify any information in an MDR.

Some of the strengths regarding MDR data are included on this slide. MDR data can provide a qualitative snapshot for specific devices and device types. These reports show how the device is used and functions in the real world, providing FDA and manufacturers with a snapshot of real-world evidence.

The data can also show us how a specific device or device type functions in a specific subgroup or population. This information can be valuable to consider during research and development of future medical devices and how those devices may affect certain patient populations.

MDR information also allows FDA and manufacturers to monitor device performance. Time-to-event and failure modes, new types of issues with improved or cleared devices, and long-term events and outcomes are all pieces of information that can be analyzed from MDR reports. This can give FDA and manufacturers clues into potential

future device modifications that would serve to better protect and enhance patients' lives.

Finally, MDRs contribute to safety signal detection and may be indicative of a larger systemic issue. MDRs can indicate off-label use, but also use errors or human factors issues that are unexpected.

Additionally, rare or unexpected events for a device or device type or a change in frequency or severity of expected events can all be catalysts for a safety signal.

These are just some of the ways in which MDRs contribute to ensuring the safety and effectiveness of devices. Additionally, this shows how important MDR information can be to CDRH's TPLC approach to medical devices. My colleague, Mr. Alex Rodriguez, will expand upon some of the strengths of the MDR program and data in his presentation on MDR analysis and trends.

As a passive surveillance system, MDRs are subject to limitations, one of which is underreporting. Underreporting can be due to a variety of factors that include:

- Device users may be unaware that FDA collects this data and the importance of reporting;
- There might be a fear of unintended consequences if the event is reported;
- There can be confusion about HIPAA privacy rules and some may think that these rules prevent them from reporting; and finally
- There is also a risk that the device malfunction or patient injury may not be clinically apparent, or it might not manifest until the patient is no longer under direct supervision of the clinician.

There are also limitations associated with the MDR regulation itself. Not all events qualify to be reported, as there are certain device malfunctions, and possibly even injuries, that do not meet reporting requirements. Therefore, it is important to keep in mind that no MDRs does not mean no problems exist with the device.

In addition, the information in the report cannot be validated and may contain incomplete or inaccurate information. Certain facts may not be obtainable from the end user, in particular, the device itself may not be available for the manufacturer to evaluate. If a manufacturer cannot obtain the device to do an investigation, a potential problem cannot be confirmed. My colleague, Ms. Jennifer Houck, will expand upon this limitation in her presentation on MDR best practices.

Lastly, the causality of the event cannot be confirmed. Many times, a direct link cannot be determined between use of a device or a malfunction and a negative clinical outcome. This is, in part, due to the many challenges associated with medical devices. There are so many stakeholders involved when it comes to medical devices, such as patients, clinicians, caregivers, etc.

There are also other things to consider such as patient comorbidities, other drugs or devices in use, the training and experience of the clinician, and the directions for use. Any of these factors can influence the outcome of the patient and typically cannot be linked to the device itself.

Despite these limitations, MDR data provides useful information about the postmarket behavior of medical devices and contributes to and may be used as a factor towards FDA's evaluation of the safety and effectiveness of medical devices.

This slide contains some available resources about MDRs and specifically, the VMSR program.

Thank you for your time and attendance today.

MR. SPEER: Thank you, Carole.

Again, I want to remind you all if you have questions and comments throughout today, you can e-mail those to oht6-feedback@fda.hhs.gov.

Now let's move on to our next presentation on MDRs best practices, and this will be

presented by Jennifer Houck. Jennifer Houck, with FDA, is a biomedical engineer/lead reviewer since 2018 in the Division of Restorative, Repair, and Trauma Devices within the Office of Health Technology 6 (OHT 6). Ms. Houck has served as lead reviewer in the review of orthopedic device premarket submissions compliance, medical device reporting, compassionate use, and COVID-19 pre-emergency use authorizations. She has also served as the medical device reporting primary focal point for OHT 6. Prior to joining the FDA, she received a bachelor of science degree in biomedical engineering from the Pennsylvania State University in 2016. She also received a master of science degree in regulatory science from the Johns Hopkins University in 2019.

MS. HOUCK: Good morning, my name is Jennifer Houck, lead reviewer and MDR reviewer in the Office of Health Technology 6 in the Division of Restorative, Repair and Trauma Devices.

Today I will be providing a summary of best practices for industry and stakeholders to follow when submitting medical device reports, which I will be referring to as an MDR for the duration of this presentation. We appreciate the opportunity to share with you tips for submitting MDRs to the Office of Health Technology 6.

Today I will be discussing the process for submitting an MDR to FDA, highlighting the requirements for who submits and how to submit an MDR, followed by an introduction of FDA forms to submit an MDR and best practices for completing these forms using FDA Form 3500A for mandatory reporting.

Mandatory reporters, including manufacturers and importers, are required to submit an MDR via an electronic submission, as summarized in the Electronic Medical Device Reporting Final Rule issued in August 2015. Manufacturer and importers must use the Electronic Submissions Gateway, which is a central point for sending information electronically to FDA. Manufacturers and importers may reference the eMDR guidance for

additional clarification regarding how to prepare and send an electronic MDR. Additional support may be provided by contacting the ESG help desk for eMDR.

Device user facilities are also mandatory reporters. They are encouraged to submit MDRs electronically, however, still retain the option to submit paper reports via Form 3500A and may reference the instructions for completing Form 3500A and guidance for medical device reporting for user facilities.

Voluntary reporters such as patients, healthcare professionals, and caregivers may submit MDRs on line through MedWatch, which is the FDA safety and adverse event reporting program. Voluntary reporters are instructed to use Form 3500 for health professionals and 3500B for patients or caregivers.

The mandatory reporting Form 3500A can be found on FDA's website for medical product safety information. This form is divided among separate sections pertaining to patient information, adverse event or a product problem, suspect products or medical device, information on the reporter, user facility or importer, and manufacturing information.

The voluntary reporting Forms 3500 and 3500B can be found by navigating to the MedWatch FDA website. Voluntary reporters are required to identify the correct form for completion by the health professional or the consumer or patient. Once completed, the form will be submitted for FDA review.

For the remainder of my presentation, I will be summarizing some problem areas identified during the review of an MDR using Form 3500A. Please note, the following recommendations and best practices pertain not only to Form 3500A, but also to voluntary reporting forms.

These forms are outlined in different sections related to aspects and information required to review an MDR. The first section contains patient information to be completed

by the mandatory reporter. Often in OHT 6, the information presented in this section are not completed but are necessary to understand the reported adverse event. For the adequate review of an MDR, we recommend that information such as the patient's age, gender, weight, ethnicity, and race are included. This information is necessary to assess a correlation between the patient's demographics and the reported event.

Section D contains information for the suspect medical device or device in question related to the adverse event. In this section, please ensure the spelling for the brand name, common device name, and manufacturer are correct, and ensure that the product code correctly reflects the suspect medical device. Consistency along spelling and product code will help FDA correctly identify the suspected device.

In addition, if known, please include the implant and explant dates for implantable devices so that FDA may determine any correlation between device life expectancy and reported adverse events.

Finally, state the device components that were paired with the suspect medical device during use in the adverse event so that FDA may assess whether additional device components may have contributed to the reported adverse event.

When completed Sections F and G, please ensure that the spelling within the facility and manufacturer are correct and consistent throughout the form.

Also ensure that the adverse event problem codes accurately reflect the device problem or health effect that is being reported in this form. Please ensure that the adverse event problem codes accurately reflect the device problem or health effect, and refrain from using problem codes that do not identify the adverse event. For example, please refrain from using codes 3190 or 3191 unless there is not enough information available to classify the device problem, clinical signs, symptoms, and conditions, or if not adequately described by any other term. In this case, the preferred term to describe the reported

adverse event should be documented in the MDR to determine whether a new term should be added to the code table, which can be found in the hyperlink provided on this presentation slide. Lastly, please identify, if any, open recalls that are associated with the suspected device or adverse event.

We also recommend that you improve the manufacturer narrative by providing additional information in Section H, Part 10 of the mandatory report form. In this example, the narrative provided information indicating a patient had been implanted with a specific device, needed revision and reported injury, however, is lacking in detail. The narrative does not indicate the issue with the suspected device, for example, breakage of the suspected device or a component.

If you are submitting an MDR for a joint replacement device, you should consider including information suggesting whether the device was cemented or uncemented, constrained or unconstrained or the -- material in the narrative. It would also be beneficial to include any details of investigation or investigation results. A detailed manufacturing narrative should be able to indicate how the suspect device was used that led to the adverse event, any accompanying device components or instruments, the issue or device problem, and the patient outcome and follow-up.

Finally, ensure that you are maintaining an adequate number of submitted reports, and be mindful in terms of under- and over-reporting. Each adverse event should require one MDR unless new information becomes available, in which a follow-up report is acceptable.

Please also refrain from reporting events where medical devices were used in animals. You are required to submit a report for a device associated MDR-reportable event involving humans when becoming aware of information from any source. Any source includes medical or scientific literature, whether published or unpublished. And as

mentioned in Ms. Wolfe's presentation, a supplemental MDR can be submitted where an investigation into the suspect device or adverse event are not completed, and can provide additional information related to the suspect device and investigational results.

Hopefully, as a result of this presentation, you are aware if you should submit an MDR either as a mandatory reporter or voluntary reporter, and to submit via electronic MDR in the Electronic Submissions Gateway or paper submission forms.

When completing either the mandatory or voluntary reporting forms, ensure that patient-level information is completed, check for spelling mistakes, use correct product codes, list the implant and explant dates for implantable devices, and ensure the adverse event, device problem or health effect codes reflect the problem reported in the form. If there is no appropriate code available, you may document the preferred term when submitting the MDR to determine whether the preferred term should be added to the code table.

Please also refer to the following resource websites for additional information and support.

Thank you. And this concludes my presentation.

MR. SPEER: All right. Thank you, Jennifer.

Again, that reminder, if you have questions or comments throughout the day, e-mail those to oht6-feedback@fda.hhs.gov.

Let's move on to our next presentation on MDRs analysis and trends, and this will be presented by Alexander Rodriguez with FDA. Alexander Rodriguez joined FDA in 2020 as a lead reviewer within the Office of Orthopedics, Division of Joint Arthroplasty, Hip Devices Team. Prior to joining the FDA, Alex worked as an engineer in orthopedic manufacturing and product development. He received his bachelor of science degree in biomedical engineering and master of science degree in engineering management from Florida

International University.

MR. RODRIGUEZ: Good morning, my name is Alex Rodriguez, engineer and lead reviewer in the Office of Orthopedics, Division of Joint Arthroplasty, Hip Arthroplasty Devices Team. It is my pleasure to provide you today with a summary on how medical device reports are used by FDA, as well as provide an MDR analysis and trending overview for several types of orthopedic devices.

How are MDRs used by FDA? MDRs are used by FDA in several ways including, but not limited to, the review, analysis and monitoring of adverse events in which we are able to review MDRs by report type, product code, year, code to describe adverse events, as alluded to by Carole in the MDR background discussion, and more.

MDRs are also used by FDA in the urgent review of death and code blue reports. We can also generate additional information or AI letters for reporters such as industry and user facilities.

We can provide action-based updates to industry, such as for recalls due to device-related failures, as well as to identify signals, also known as information that negatively alters or impacts the perceived benefit-risk profile of a marketed device since that it may lead to new or increased risks or reduced benefits. For example, this can be a spike observed in the number of MDRs for a device, a new product failure mechanism or mode causing patient harm, or new risks introduced by off-label use.

Furthermore, signals are not only derived from MDRs but also other sources such as post-approval studies, inspections, literature or registry reports. In fact, a search of the last 30 active safety signals within CDRH, the Center for Devices and Radiological Health from October 2019 to date, revealed that MDRs has been one of the original sources in 50% of these signals.

All of these points highlight the important role of MDRs and underline the need for

high-quality medical device reporting which can ultimately lead to better patient outcomes.

As a disclaimer, I would like to note that we performed analysis and trending for certain product codes. However, the information presented may not be an exact representation of MDR trends since elements such as inappropriate product codes or adverse event problem codes may have been entered in the MDRs and ultimately included in the data analyzed and presented today. The information on data presented is for illustration purposes on how FDA can use MDR data, and not meant to indicate any action items forthcoming from FDA.

So to provide an overview of MDR analysis and trending, we identified several product codes that encompass our Office of Orthopedic Devices. We searched and compiled data from our internal MDR database for that past 3 years from 2018 to 2020 and extracted the top adverse events related to two code types; the first one, health effect-health impact, or the consequences of the medical device adverse event incident on the person affected, as well as medical device problem such as malfunction, deterioration of function or failure.

The first product analyzed was JWH, related to knee joint semi-constrained cemented prosthesis. The graph on the left-hand side of this slide shows a number of MDRs from 2018 to 2020 and, as you can see, there is a slight increase in MDRs submitted from 2018 to 2019 and a decrease to about 12,000 MDRs submitted in 2020, lower than MDRs submitted in 2018.

We conducted an analysis of the top three health effect-health impact codes and medical device problem codes for JWH from 2018 to 2020 and the results are presented in the tables to the right. Please note that the number following each health effect-health impact and medical device problem represents the number of times that code appeared in our search. It was noted that the codes for pain and infection were a top three health

effect-health impact code; however, there's a pattern observed that the code for "no code available" was also identified by reporters as a top three problem code. This may be attributed to many reasons, including those described by Jennifer in the best practices discussion, where it is possible that reporters may be unsure of the code that specific adverse events fall under.

Regarding medical device problems, we observed that fracture and loss of or failure to bond were top three medical device problems; however, it was also observed that adverse event without identified device or use problem is observed as a top three problem code in each of the past 3 years. Similar to the table above, an emphasis on identifying the most appropriate problem code is critical in order for FDA to better analyze problems related to patients and devices.

This is an example of something FDA may monitor, and we recommend working together to better identify adverse events which will in turn assist FDA when reviewing and analyzing MDRs.

Product code HWC is related to smooth or threaded metallic bone fixation fastener devices. Here we can see an upward trend in MDRs submitted from 2018 to 2019 with a slight downward trend from 2019 to 2020. It was noted that the codes for pain, infection, and failure of implant were a top three health effect-health impact code for HWC from 2018 to 2020. However, there's also a pattern observed that no code available was identified by reporters as the top problem code every year.

Once again, FDA is here to assist you and we urge you to implement the recommended best practices discussed earlier in order to replace codes such as no code available with an accurate description of adverse events.

Furthermore, unspecified infections, pain, and failure of implant may potentially be the top reported codes should the events identified as no code available be appropriately

assigned a code that identifies the effect and impact to the patient.

Regarding medical device problems, we observed that break, fracture, migration, and device-device incompatibility were in the top three medical device problems from 2018 to 2020. However, adverse event without identified device or use problem was trending as the top code from 2018 to 2020. Similar to the previous product code discussed, an emphasis on identifying the device from the event is critical so that FDA can better analyze device-related problems.

Product code LOD is related to PMNA bone cement. Here we observed that the number of MDRs submitted in 2019 is about double that from 2018, followed by a drop back to roughly the number submitted in 2018, observed for 2020, which could have easily been attributed to the COVID-19 pandemic, for example.

Furthermore, the top three health effect-health impact analysis revealed that reporters had been able to identify specific codes such as pain and edema for events related to LOD devices. However, the code for no code available was once again identified by reporters as a top three code in each of the past 3 years.

Regarding medical device problems, loss of or failure to bond and loosening of implant not related to bone in-growth were two of the top medical device problems in the past 3 years. However, adverse event without identified device or use problem was once again trending as one of the top three codes.

Product code NKB is related to thoracolumbosacral pedicle screw system devices. In each of the last 3 years we observed that the number of MDRs submitted has slightly increased every year. In this case, this is something we would monitor since such a trend may indicate a variety of issues which may be significantly affecting the patient as a cause of a device or other underlying issue.

In addition, you may have noticed the numbers of MDRs submitted varies, at times

significantly, when compared to other products discussed, and this may be due to different types of products such as standalone or implanted as a system with multiple components and articulations which may lead to a lower or higher number of adverse events submitted.

It was noted that the codes for injury and spinal column injury were the top three health effect-health impact codes in the last 3 years. However, we once again observed that the code for no code available was identified by reporters more than any other code.

We also observed that the reporters are identifying no known impact or consequence to patients, which indicates that manufacturers are concluding that the adverse events result in no harm to the patient.

Regarding medical device problems, break and adverse event without identified device or use problem is observed as two of the top medical device problems within the last 3 years, and we once again emphasize to make your best effort to identify the device from the adverse event. The other defined problem codes in the table illustrate a specific correlation between the adverse events and the device.

In addition to product code MDR trending, we conducted a time-to-revision analysis for product code NKB, discussed in the last slide, pertaining to the thoracolumbosacral pedicle screw system devices. The reason behind this analysis is to provide another example of how FDA can use MDR data. Here we would like to share some of the patient and medical device problems identified that may be contributing to the periods of time from the original implantation to the time a revision was performed for this device type.

This information is important for a variety of reasons, including it can provide us with a glimpse of certain life expectancies for different devices. This information can also give us an idea of what may be occurring within the first few months or few years in the life of a device, which may raise questions of safety and effectiveness depending on specific patterns observed, that is device related, for example. In the case of NKB devices, for all

MDRs reviewed from 2018 to 2020, it was observed that roughly 1,500 revisions occurred within the first year with that number significantly dropping every year thereafter. We also identified the health effect-health impact and medical device problem codes associated with revisions which occurred within the first year. It was noted that codes for no known impact or consequence to the patient, pain, and failure of implant were in the top three codes for health effect and health impact. However, no code available was once again identified, and we highly recommend reviewing and implementing some of the best practices discussed earlier so that we can together initiate any actions to identify and mitigate these adverse events.

In the case of medical device problems for revisions that occurred within the first year, we observed that material deformation is the top code and we encourage industry to note this and look at whether your devices fall within these reports so that you can create action plans to address these issues.

I would like to thank our team members for their participation in the MDR analysis and trends effort.

In conclusion, although we've provided an overview of MDRs, touched on best practices such as how to more appropriately identify health effects and medical device problems, as well as an overview of how FDA uses MDRs and trends which our office has observed, we encourage every company to consistently conduct continuous improvement on the various elements within your quality management systems in an effort to enhance those processes which you influence, in order to reduce the overall number of MDRs. We understand that this is something that is easier said than done, but which can be accomplished by enhancing the level of communication and collaboration with all stakeholders internal and external to your company.

That concludes this presentation. I thank you very much for your attention and we

look forward to a continued partnership with you to further improve the quality of medical devices and together facilitate better patient outcomes.

MR. SPEER: All right. Thank you so much, Alex.

Folks, this is a lot of great information and I hope you're getting a lot of out of this, as much as I am. So we've got a few more sessions, we do have a break coming up here soon, so hang in there. But again, if you have questions throughout, I want to remind you to submit those via e-mail to oht6-feedback@fda.hhs.gov.

Let's move on to some of our industry representatives today, and the first session on that will be industry perspective on MDRs and recalls, and this will be presented by Stephanie Matthews and Kara Ditty-Bovard; both ladies are from Johnson & Johnson.

Stephanie Matthews serves as the quality system director for field actions and product issue escalations for hospital, medical device businesses, Johnson & Johnson based in Cincinnati, Ohio. For the past 3 years she has led a team supporting FDA recall submissions and interactions ensuring compliance standards for FDA requirements and processes through field action closure. Stephanie has over 20 years of experience in the medical device sector, spanning various roles within postmarket surveillance, pharmacovigilance, quality systems, quality engineering and supplier quality engineering, and new product development and sterile packaging development. She earned her bachelor's in packaging engineering from Michigan State University and an M.B.A. from Xavier University, Ohio.

Our other presenter is Kara Ditty-Bovard, also from Johnson & Johnson. She is the director of health authority reporting within Johnson & Johnson Hospital Medical Devices. Her current responsibilities include leading the FDA and AE teams charged with reporting AEs and malfunctions. Kara has over 20 years of industry experience working in both the pharmaceutical and the medical devices sectors. In prior roles, she has worked in vaccine

manufacturing, clinical packaging, pharmacovigilance, product release, quality complaint handling, and event commercial teams.

MS. MATTHEWS: Hello, everyone. My name is Stephanie Matthews, Quality Director of Field Action and Product Issue Escalation for Johnson & Johnson Medical Devices. I will be sharing a device manufacturer's perspective and information regarding medical device recalls.

The primary objective of a field action is to safeguard the public from harm. The secondary objective is to address products found to not be meeting applicable regulatory requirements. It is important to execute established procedures while performing periodic reviews of those procedures to confirm compliance with internal and external requirements.

Some of the effective QMS requirements and procedures include reporting to affected health authorities and notified bodies. It is important to have processes for communication, dissemination, notification, and response to worldwide health authorities and notified bodies according to local regulations, where treating and segregating product impacted may be required therefore preventing further distribution as required by the notification.

It is important to secure and reconcile all nonconforming product. It is also important to ensure effectiveness checks are conducted, corrected actions and preventative actions to prevent recurrence are implemented and effective, and regular status updates on the recall are provided to local health authorities. It ensures continued communication after the recall initiation through closure.

An important factor to consider is if the field action will alter the standard of care or create an issue where there is no substitute products and surgeries cannot be performed. Manufacturers should assess if the field action will create a market shortage. If a market

shortage will occur, determine how this will be handled, discuss with FDA early in the field action strategy, and communicate to impacted consignees through an applicable communication package. For example, if a manufacturer can no longer supply a particular device, product alternative or substitution in the field action notification can be provided to support continuity of care with support determined by medical safety. Let's now review information included in the field action communication.

Field action communication is to convey: starting with description of the problem and providing potential health hazards associated with it. You should specify the reason of why the field action has been initiated. Make it clear whether the risk is to the user, the patient or both. You should also try to indicate if there is any residual risk when executing the notification or removal.

It is also important to include the product in question and is subject to the field action notification or removal. Review information regarding the scope of the field action. The scope will include some of the following information depending on the field action type:

- The name;
- Product code;
- Lot or serial number;
- Manufacturing date;
- Quantity distributed;
- Expiration date; and
- The UDI/TTIN numbers.

If the depth of the field action includes second-level consignees, these should be identified as second level or indirect when communicating to FDA or notified bodies. These second-level consignees are customers who purchase from first consignees, which could

include hospitals, surgery centers, doctors' offices.

It may be required to return product to the manufacturer for segregation and destruction. Information will be provided to physicians through the health hazard evaluation describing the situation and the clinical use context of the issue.

Analysis conducted by a qualified medical professional within the device manufacturer to determine the potential impact of a product quality issue on the patient's health and safety, including risk-benefit analysis, is included in the HHE. Impact of the recall on the treatment of patients, any risks to public health, impact to product supply, the availability of replacement product and alternative therapies are also considered within the health hazard evaluation.

Some practices to consider include discussion of the situation, the clinical use context, and any related clinical factors that could influence the outcome. The HHE will discuss reasonable and foreseeable direct or indirect harms including any potential harms resulting from the impact that a recall would have on the treatment of patients or at an individual or public health level.

The HHE should also be used to describe the potential impact or harm to the patient or user. It would also describe the severity of each harm and the likelihood that each harm will occur when the situation is present.

Other factors to consider are how special patient populations may be affected, such as age, sex, comorbidities, will impact the severity and likelihood.

In the recall communication, information will be provided and shared with physicians on relevance to any potential impact to patient care and postoperative care, if applicable. For example, an orthopedic implant recall removal based on clinical relevance, factors, and severity may not impact or affect the standard patient follow-up, if implanted. This would be provided in a recall communication to the physician. Medical device manufacturers do

not have access to patient information due to HIPAA requirements for patient confidentiality. However, manufacturers work closely with physicians, hospitals, and FDA to ensure understanding of the issue and if standard of care and patient monitoring is altered.

Finally, discussions with the recall office at FDA can aid in the understanding of the device design, understanding of the issue, understanding of the nonconformance impact, and, when necessary, medical-to-medical conversations and discussions with the manufacturer and Agency can be extremely helpful in the understanding, the development, execution of the recall strategy.

Thank you.

MS. DITTY-BOVARD: Hello, this is Kara Ditty-Bovard. I am director of health authority reporting for Johnson & Johnson Hospital Medical Devices. Today I'm pleased to be talking with you about medical device reporting from the perspective of industry. I will cover several topics that can be challenging for even the most seasoned complaint-handling team.

The first topic I would like to cover is product returns. Getting products returned for evaluation and completing a thorough investigation of the complaint allegations are, of course, closely linked. However, as we all know, getting medical devices returned can be difficult. The device may be implanted, it may have been discarded, or the customer may simply refuse.

So what do you do as a manufacturer to thoroughly investigate? On the slide I've listed some practices to consider. First, always complete three follow-ups to assure due diligence in requesting the return. Second, consider working closely with your field-based teams to leverage relationships they may have with the HCPs involved in the allegation. Where the device is implanted, it sometimes helps folks to request photographs, X-rays or other images that may be available. And another thing to consider is, for devices that are

returned for maintenance or service on site, consider having the technicians trained to identify and document potential malfunctions.

When completing the 3500A, make sure to complete the suspect medical device field to clearly show if the device is still implanted and make sure to supplement this information in the H-10 if, for instance, the device is a serviceable device that is in use or if the customer has indicated that they have discarded the product in question.

As we discussed, getting devices returned can be difficult and unfortunately, can be a frequent occurrence for industry. So how can industry move forward to investigate without a device? There are several practices to consider. You can request an interview with the HCPs involved with the complaint. Hopefully, they can provide more detailed information about the event and the functioning of the product. You could always request a device manufacturing record review. You can complete a search for nonconformances and/or CAPAs that may be related to the defect. You can request an evaluation of any retained samples, if they're available. Another avenue is also to take a look at the occurrence rate, what's happening as far as the defect levels at the time of the event compared to the expected rate for the product and defect combination.

While all of these could eliminate a potential root cause for the complaint, it is a good practice to note any limitations for each in your investigation summary. When completing the 3500A, make sure to tell the story of your investigation, what was reviewed and what the outcome was, in a manner that links back both to the event conditions and any codes that you've chosen for the 3500A.

Another common challenge for industry can be determining whether a device is suspect or concomitant. Remember, concomitant devices are used at the time of the event but are not thought to be involved in the event. They are identified on the 3500A along with the suspect device. Any device with the potential to be involved in the event should

be considered suspect and would need to have its own 3500A form submitted. I would suggest the following: consider using clinicians with practical experience actually using the devices in a clinical setting to determine if the product is suspect or concomitant. Where you have constructs that consist of multiple devices, you need to be very careful when you evaluate those as they may require multiple 3500A forms for each suspect product. And if there are multiple suspect products in one complaint, have a clear process on how to link these complaints.

Another common challenge for industry is the identification of off-label use or use error and understanding how they may have caused conditions that led to the complaint. When working with these types of issues, it can help to pull apart the analysis of the event into two separate paths.

First, really dig into what happened. Ways to do this are to request interviews with the HCPs involved with the complaint to gain a deeper understanding of the event or consider working closely with field-based teams because they may be able to talk to HCPs on your behalf or even may have knowledge of the event itself.

The second thing to consider is how important it is to understand the boundaries for use your organization has defined for the product. Two ways to do this, of course, are to look back at the IFU and to have a look at your risk documents.

I think it's important, when you're writing these up, to carefully consider the language used to describe the event when you're filling out the 3500A in the manufacturer narrative.

The next topic I'd like to talk about briefly is literature articles. They can, of course, provide valuable information about the performance of medical devices. It is important when you're dealing with literature articles to clearly define how you will process articles to ensure the potential value is realized.

Here are some things to consider. Follow up with the author as needed to get details on events, patients, and device specifics that may not have been clear in the published article. Work closely with teams within your company also assessing articles to assure calibration on identification of events, patients, and device specifics. I'm thinking specifically of postmarket surveillance teams, teams that may be using them for PSURs and R&D mining that may be going on to understand the product. You should really consider carefully defining boundaries when necessary to report as your product -- for example, when the device is described without a brand name associated with it. We all live in a world where you may find an article that refers to a nail or a screw; it's hard to know if that's your nail or your screw, so think about carefully defining that.

I would suggest considering special training for teams tasked with reading and coding articles. This is really difficult work, it takes a lot of training, so specialized teams may be very helpful for dealing with literature articles. And of course, don't forget to identify literature articles on the 3500A in the report source, they require a different approach and it will help anyone reading the 3500A to know the source is literature.

The next topic I'd like to spend some time on is product end of life. Device end of life is another situation that may lead to gray areas when assessing complaints. To assure teams can best handle complaints where product performance may be related to end of life, it is important that the complaints team has strong product training and also has access to clinicians that can assess the event for relatedness.

Some additional items to consider are making sure the team knows if end of life is labeled for the device, referring back to the IFU as appropriate for information that may be in there about end of life. It's always helpful to go back to the risk documents and see the approach that was designed for the product. And I would suggest including any end-of-life information with reportable events where the product is at or past end of life.

So we're to my last slide in our whirlwind tour of "all things medical device reporting" and I have one final tip to share, that is to avoid selecting "code not available" when completing the 3500A. There really are hundreds of codes available for every place you need to enter a code and so it should really be a rare occurrence to use "code not available." I would even suggest that it should take management approval to use it on the 3500A. And if you're unsure about what to do or if you can't find the right code, it's always acceptable to reach out to our friends at the FDA. I know from experience, they will always help.

Thank you so much for your time.

MR. SPEER: Thank you, Stephanie and Kara.

Let's move on to our next presentation on patient perspective on MDRs and recalls, and this will be presented by Richard Seiden. Richard Seiden is a retired partner and healthcare business lawyer with Foley and Lardner, LLP, in the Los Angeles office. His practice focused on all aspects of healthcare business counseling for healthcare providers including formation of business entities, general business, and financial matters and mergers and acquisitions. Mr. Seiden is a former member of the firm's management committee and previously served as the managing partner of the firm's California offices.

Mr. Seiden has been peer-review rated as AV Preeminent, the highest performance rating in the Martindale-Hubbell's peer-review rating system. He has been listed in the *Best Lawyers in America* every year since 2006, and *Chambers USA: America's Leading Lawyers for Business* from 2008 to 2011. Mr. Seiden was also selected for inclusion in the 2009 through 2016 *Southern California Super Lawyers* lists.

Richard.

MR. SEIDEN: Thank you. Today I'm here as a volunteer patient advocate. I have had severe psoriatic arthritis since 1976. Over the course of time I have had multiple joint

replacement surgeries of both knees, both hips and both shoulders. I serve as the chair of the Public Advisory Board to the American Joint Replacement Registry. Fortunately, I have not experienced any recalls of any of my devices.

So in preparation for this panel, I conducted two interviews. One was with a patient with recalled hip implant, in whom the device remains implanted to this day, and the second was an interview with a Patient Safety Action Network representative. I'll refer to them as PSAN. It is a coalition of individuals and organizations consisting of patients who have been medically harmed, your loved ones, and concerned advocates. Her responses were based on interactions with patients. The questions in the interviews covered issues surrounding orthopedic devices and recalls. Next slide, please.

Question 1: What details did the doctor give you about the device before it was implanted? This is totally dependent on the thoroughness of the surgeon. The recall patient received extensive information about possible outcomes, dislocation, possible failure. Based on her conversations with patients, the PSAN representative felt that pre-surgical consultation is typically inadequate to enable a patient to make an informed decision. There was no discussion of materials, the possible metal interactions, etc. It was remarkable how much better the recall patient's experience was than what the PSAN representative described. In my personal experience, the details and the decisions are quite complicated, probably beyond the mechanical understanding of most patients, and I'll get to the detail of that later.

Question 2: Were you aware of how your device was performing in others before it was implanted? I personally do not recall discussing that. The recall patient was told of other patients' experience with the device. The PSAN representative expressed concern about the American philosophy that newer is always better but that may not be appropriate for a particular patient. She noted that there were many variables in device choice

decisions and oftentimes established devices worked better than new ones.

Question 3: How did you become aware of the device recall? Once again, I didn't experience this. The recall patient received written notice and including notice from the manufacturer, it suggested the testing for metals, so she and her physician -- surgeon conducted blood tests and X-rays and determined that her implant could remain in place. Next slide.

Number 4: What was your initial reaction? The recall patient had conversations with the surgeon who, as I said, recommended blood tests and X-rays. However, there was no issue with respect to her particular device, so the device remains in place. The PSAN representative felt that the typical reaction of a patient would be to seek immediate removal of the device, but she noted that that may not be the best approach unless there is a systemic problem as a result of the device. Otherwise, it may be more dangerous to remove it.

Number 5: How did your talk with the doctor go once you found out the device you have implanted has been recalled? The recall patient was extraordinarily satisfied with the conversation and the testing results, so there were no changes. Of course, this is dependent upon the continuing availability of the surgeon, so hopefully there will be a replacement surgeon available to talk to a patient under these circumstances.

Number 6: What information were you provided about the recall? The recall patient was told in the manufacturer's letter what other patients were experiencing, what symptoms could be observed, and how to monitor for any future damage from the device. Next slide, please.

Number 7: Were you happy with the level of detail you were provided? The recall patient was satisfied with the detail from the manufacturer and particularly satisfied with the surgeon. The PSAN representative had no real answer to this question, but hoped that

the level of detail was adequate to enable the patient to make the right decision.

Number 8: What was the plan for monitoring you? The recall patient said metals tests and X-rays and follow-up calls with the surgeon. The PSAN representative thought there should be explicit advice from the FDA, and the primary care physicians and cardiologists should also be part of the monitoring of the patient going forward. Therefore, the patient needs to alert other physicians of the recall because the patient was the only one who knew who those other providers were.

Number 9: Are you aware that information on device recalls and adverse events is public and can be found on the FDA website? Yes, I personally have come to learn that this information is readily available. The recall patient felt that she was aware of all of this because she had done extensive online research both before her surgery and when she got the recall notice. The PSAN representative felt that the FDA needs to issue more public information with details beyond raw data that is capable of being understood by the typical patient, and in language that is understandable. Next slide, please.

Question 10: If not, had been you aware of it, would you have considered it in your decision making regarding that particular device? Although I did not experience a recall, if I were aware of one, I should have -- I expect that I would have asked for an alternative device. This is an excellent example of where shared decision making should occur. The recall patient did not seem concerned, she was aware that the device could wear down and could have complications but she was so desperate to have her implant that she was willing to take risks greater than, I think, the typical patient might. But she also was far better informed before the surgery based on her own research and observing YouTube videos of her surgery as to what the surgery would entail.

Number 11: How can the Agency, industry, and healthcare providers improve regarding alerting patients to the problematic devices? In my opinion, social media may not

be adequate given that many devices are implanted in seniors who may not have access to social media. The recall patient thought the letter and her surgeon contact were adequate. The PSAN representative felt that there should be a system for broad public outreach, perhaps through Medicare or AARP in addition to the FDA, and that there should be a similar system for medical device recalls similar to automobile warranties and recalls. It is possible that the recall information could be included in the patient version of the AAOS registry annual report, but it is something for limited distribution to the orthopedists, so that may not expand the communication very much.

Number 12: Was there a difference in the amount of information and detail originally presented versus after the recall? The recall patient claims to have asked a lot of questions prior to the surgery, she watched YouTube, as I mentioned, so she didn't believe that the amount of information was much more detailed in the recall notice than what she had in advance of her surgery, which sounds atypical to me. Next slide.

Number 13: Did your surgeon disclose how long the device has been on the market at the time of the surgery? In my experience, no. The recall patient was given a fairly new device and she knew it, and the differences from older devices, and understood all of the risks and supposed benefits from the device. She claims to have had a full discussion with her surgeon. As I said, this sounded to me like an atypical experience with a better educated patient than a typical patient.

Number 14: Was the labeling you were provided clear and understandable? Personally, I never received any labeling for any of the six devices that are implanted in me. I would have liked to have received the labeling, provided it was written in readily understandable language. The recall patient was not given the labeling. The PSAN representative says her organization recommends that patients ask for the labeling information either before or after their surgery.

Fifteen: What details were you given about the procedure and what options were discussed? After physical therapy was not adequate alone, I received a general description of joint mechanics and device mechanics, postoperative recovery and expected range of motion. The recall patient, as I said, had an extensive and thorough discussion with her surgeon about the mechanics. He apparently made hand-drawings of the joint and the device, it sounds like she was very prepared for that discussion. Next slide.

In summary, there were three completely different perspectives based on the relative experiences of the patients.

Before my surgery, I relied very heavily on the references I received from my orthopedist and as a patient, to me, you have to have ultimate trust and confidence in your surgeon because, as I said, I don't believe the average patient can understand all of the decision making that goes into which device is chosen and which procedure is chosen for any particular patient.

However, in hindsight, reflecting back, I should have asked the orthopedist for a lot more detail about the procedure, the device, and post-surgical expectations, so I could have been better informed and participated in more of a shared decision as to my medical care. I never received any packaging and frankly, do not know the manufacturer or component materials of any of my devices. But once again, fortunately I have not had any device recalls. Wouldn't know whether they were relevant to me if I did. Next.

I've tried to summarize some suggested potential improvements to the system here. This includes input from the PSAN representative. As I wrote, the FDA should consider an action plan for orthopedic device recalls, setting forth explicit requirements for the manufacturer notice of the recalls and particularly those communications that are passed on to patients. It should specifically include who the patient should contact for more information, and that's particularly true if the patient is no longer in contact with their

surgeon, because oftentimes these relationships between patients and orthopedic surgeons are sort of one-and-done.

There needs to be very clear instructions to the patient and the surgeon for follow-up clinical visits. Specific instructions as to what should be monitored as a result of the recall, whether it's blood tests, X-rays, MRIs, etc.

A reporting system for surgeons so there can be post-recall surveillance by the manufacturers and the FDA. Once again, the PSAN representative came up with the idea to create a system similar to automobile warranty recalls for better follow-up.

And then also, perhaps expand the communications with regards to primary care physicians and cardiologists to include the possible consequences of a device recall.

And there may well be a role here for patient registries or orthopedic registries with respect to recall of devices.

Just a last slide. Two personal observations regarding my medical care -- sorry, next slide -- that patients need to be advised that there are limits on what they can have in the way of MRIs after their surgery because of the metal in the devices and the interference with the MRI pictures or images after the surgery.

I noticed that there are some interesting intergenerational issues among orthopedic surgeons. Several times I have been to young surgeons who can easily diagnose a problem but tell me that they don't do the surgeries that are necessary because they are not experienced with arthritis patients. This appears to be in part a result with respect to rheumatoid arthritis-like patients, that the biologic drugs have prevented a lot of the surgeries for this type of patient. So if they've been trained in the last 5 to 10 years, they may not have the experience or education in that area.

And finally, it appears as if there are a limited number of orthopedic surgeons who are good at performing revision surgeries if a device is recalled and needs to be explanted.

So perhaps as part of the notice, there could be a list of orthopedic surgeons who perform revision surgeries and from what I know, oftentimes these are academic orthopedists.

Thank you very much, that's the end of my comments.

MR. SPEER: All right. Thank you so much, Richard.

Folks, we're going to make a slight adjustment to the planned agenda. We're going to take a break now, so please come back at 5 minutes before the top of the hour or at 10:55 a.m. Eastern Time. When we come back from break, we'll do the next Menti survey and then after that we'll get into the group discussion. So right now we're going to take a break and see you back in a few moments.

(Off the record at 10:48 a.m.)

(On the record at 10:55 a.m.)

MR. SPEER: All right, we're back from the break. Now's the time for our next Menti survey today and this will be presented by Ting Song from FDA. Dr. Song has been serving as the assistant director in the Division of Joint Arthroplasty Devices, Knee Arthroplasty Devices Team within the Office of Health Technology 6 at FDA since 2019. Dr. Song is a biomedical engineer who served as a lead reviewer at FDA since 2012 and acting deputy division director in 2018 and '19 of DRH within the Office of Health Technology 7. She received her Ph.D. in biomedical engineering from Columbia University. Dr. Song is an expert in both premarket and postmarket compliance submissions, who performed foreign inspections in the past and trained FDA inspectors.

Dr. Song.

(No response.)

MR. SPEER: Dr. Song, I think you might be on mute.

(No response.)

MR. SPEER: It was about the Menti survey and I think we've got some technical

difficulties.

So with that, we're going to go ahead and proceed with the group discussion for Session 1. Let me introduce the moderators and panelists for this group discussion, representing perspectives of both industry and FDA. So first, let me give brief introductions of the moderators.

John Gomes from FDA holds a bachelor's degree in electrical engineering from the University of Maryland and a master's degree in electrical engineering from the Johns Hopkins University. He joined CDRH in 2012 as a compliance officer. Over the past 9 years he has led various mission-critical compliance projects involving dental, ENT, ophthalmic, and surgical devices. Prior to joining the FDA, Mr. Gomes worked in the private industry for over 9 years as an electrical engineer. His work involved design and characterization of various electrical, optical, and optomechanical sensor systems.

The other moderator is Linda Braddon with Secure BioMed Evaluations. She's the president at Secure BioMed Evaluations and works with both emerging and established companies to prove regulatory quality and technical support for both the medical device and biologics industry. Dr. Braddon holds a bachelor of science in engineering from Mercer University School of Engineering along with a master of science and Ph.D. in mechanical engineering with a specialization in bioengineering from the Georgia Institute of Technology. She served as a National Science Foundation fellow at both Duke University and Georgia Tech and won the 2009 Women in Technology Small Company Woman of the Year Award. Additionally, Dr. Braddon is on several industry specific boards to keep abreast of changing currents. Dr. Braddon founded Secure BioMed Evaluations to provide strategic support to the medical device community.

And now let me introduce the panelists. James Walker from FDA was born in Charleston, South Carolina. Being an inquisitive young man, he later studied and received

degrees in physics and engineering from the University of South Carolina and South Carolina State University. Interested in the life cycle of medical devices, he joined FDA and has become a valuable resource in the medical device electronic product areas. Currently, Mr. Walker is the assistant director of Recalls and Shortages Team within the Office of Regulatory Programs in CDRH.

The next panelist will be Michelle Rios from FDA. She's the assistant director of the Medical Device Reporting Team in the Office of Regulatory Programs from CDRH within FDA. Ms. Rios received her undergraduate degree in microbiology from the University of Puerto Rico, and her graduate degree in biotechnology from Johns Hopkins University.

The next panelist is Jennifer Harris. Jennifer is the director of quality assurance for OsteoMed/Acumed based in Addison, Texas. She has worked in the medical device industry for 20-some plus years. Some of her experience includes roles focused in active implantables, sterilization, diagnostic equipment, OR capital equipment, and orthopedics. She received her bachelor of science in engineering science and mechanics from the University of Tennessee.

The next panelist is Erika Guthrie. Erika is the director of quality for Acumed/OsteoMed. She worked in industrial engineering prior to her 13 years of medical device industry experience. Some of her areas of focus have been in process validation, statistical analysis, and design assurance. She holds undergraduate degrees in both industrial engineering and mathematics, as well as graduate studies in statistics.

Rounding out our panelists are presenters from earlier today, who will be Richard Seiden, Stephanie Matthews, and Kara Ditty-Bovard.

So let me hand things over for the group discussion to the moderators.

MR. GOMES: Good morning, everyone, and welcome to the Session 1 group discussion. My name is John Gomes, I'm a lead reviewer in the Office of Orthopedic Devices

in CDRH, and it's a pleasure to be able to moderate this session of today's public workshop. I also have the pleasure of having Dr. Linda Braddon from Secure BioMed Evaluations as another moderator during this group discussion.

Good morning to you, Linda.

DR. BRADDON: Good morning. Thank you for allowing me to participate.

MR. GOMES: Absolutely. So Session 1 is focused on MDRs and recalls and --

(Audio malfunction.)

MR. GOMES: My apologies, I was having some Internet issues. So Session 1 is focused on MDRs and recalls and hopefully, everyone had an opportunity to listen to the presentations this morning and I hope that they provided some background on MDRs and recalls for those who may not be familiar with these processes, and some additional clarity for those who may be familiar with them.

I would also like to thank the Session 1 panelists, Nick Walker and Michelle Rios from FDA, Stephanie Matthews and Kara Ditty-Bovard from Johnson & Johnson, Jennifer Harris and Erika Guthrie from Acumed/OsteoMed, and Richard Seiden, who will be providing the patient perspective on these two topics.

At this time I would like to remind the audience that we welcome and encourage any questions you may have about MDRs and recalls. Please send your questions by e-mail at oht6-feedback@fda.hhs.gov. We are actively monitoring this e-mail inbox for your questions and as your questions arrive to us, we'll try to include them in the discussion.

With that said, let me begin this group discussion with my first question to the medical device industry and in some respects, also FDA in the panel. The first question is, as we have seen in the presentations, oftentimes MDRs are submitted with no code available or saying that without any devices identified. What are the challenges that may cause this to happen? And besides urging manufacturers not to use 3190 or 3191 as much

as possible, are there additional recommendations for overcoming these challenges?

I do have a second part to that question, I'll repeat it. I'll state it now, but I am happy to repeat it at a later point during the discussion. The second part reads: What kind of challenges do incomplete or unreliable data present for decision making, both from the business side and the regulatory side? In other words, if the data was more complete and reliable, what kind of additional analyses or decision making can be done with them?

MS. DITTY-BOVARD: So this is Kara from Johnson & Johnson, maybe I'll jump in from the industry perspective on the question about coding. Just a quick check, can everybody hear me okay?

MR. GOMES: Yes, thank you.

MS. DITTY-BOVARD: Cool. I think coding can be a challenge to get the right things in the right places. I think it takes a lot of training, we really focus on training first, first and foremost, to make sure people are really confident before we set them loose on their own about what needs to be done in, you know, for each section of the form.

One of the other approaches we take is to not actually have our teams use FDA codes, so we use common terminology and have them mapped on the back end, so there are lots of choices available to the teams that will match the language that they are seeing in reports and then we have chosen to map them on the back end. So I think that makes it a little bit easier because you can find those words that you see in reports or in literature articles and then the system actually says okay, this maps to this FDA code because you may have lots of variations that actually map to just one FDA code. So that's an appropriate -- to help with that.

DR. BRADDON: Could I ask a question on that?

MS. DITTY-BOVARD: Yes.

DR. BRADDON: When you have the internal mapping, that is something your

company has developed, correct? Like, your team has gone through the wording and then mapped it to a specific FDA code. For small companies who have a much smaller team than like J&J, what do you feel are best practices to develop that, understanding their human resource aspect is probably much smaller?

MS. DITTY-BOVARD: Yeah. So I think, you know, my questions always -- my answers always have to be couched. I come from a really big company, right, so that's a great question. When you're small, you don't have the advantages of having maybe a bunch of physicians who can help you map all of those codes in a big system that allows you to do stuff like that.

I have worked at smaller companies and there is an advantage to that, too, in that the number of products is smaller and so you can know those products really well and you can know everything about those products, you know, you can really be an expert on those. So I would think, from a small company perspective, it's about creating that product knowledge and understanding what we see with our products, we're going to receive the same complaints over and over again and so just say these are the things we see 80% of the time and develop at least some kind risk document that says these are the codes we see frequently and these map to these FDA codes. A cheat sheet, I would suggest, I think, could be an easier way to do that. Less resource intensive.

DR. BRADDON: Great advice.

MS. HARRIS: I can add to that a little bit. Hi, this is Jenny from the OsteoMed/Acumed group, and we have a bit of a smaller segment, I would say, in comparison. As you mentioned, we do have a smaller team working on this that makes for, I think, a closer-knit group on a familiarity with what we're coding. I wouldn't say our product offering is smaller, but there is a repetitive nature to the things that we see to a certain extent, so that is what we do. And when things come up that are unusual, then that

kind of smaller team can quickly gather and walk through and again set up a new template for what we've seen so that the next time, if that comes around, we can walk through it.

MS. GUTHRIE: Yeah. And adding to what Jenny was saying -- this is Erika Guthrie -- in our system we do have "cheat sheets" that we have to look into that coding. They're built up over time, so we have a lot more personnel know-how building those things up and we need to make sure that we really document all of that pretty well because we do have smaller teams.

MS. RIOS: And I was going to ask, as you are evaluating your processes and changing it based on the new coding structure, are you considering the levels of hierarchy when it comes to determining or identifying the correct coding? We often recommend that as you submit your adverse event reports that you select the lowest level of coding. How is that incorporated?

MS. DITTY-BOVARD: Yeah, we've proceduralized that from a J&J perspective, just to line up with guidance and the regulations, that coding has a priority to it and that's how we train our teams.

DR. BRADDON: Does FDA have resources on the Internet on their learning program? There's lots of great learnings on the FDA website. Again, for a small company, right, who might be training people for the first time, are there resources out there that FDA considers best practices for training folks on selection of those codes?

MS. RIOS: In our website we do have the codes available in our enhancements coding page. That is something that we can look into as we recently completed that back in March, earlier this year in March, we completed the reharmonization with IMDRF for adverse event coding.

DR. BRADDON: It would be really helpful, again -- and I'm coming at it from a small company perspective -- to have a video that walks through the form, the expectation of

what FDA ideally -- best practice -- would like to see and just maybe some best practice tips and tricks on selecting those codes. And one of the questions that came across from the website address was if you have a product with two components for an issue like infection, does a company fill out two forms? So maybe guidance on how to do it.

MR. GOMES: Okay. So I have a question for -- we received a question on the recalls and I was wondering if Nick could kind of help us discuss that. There appears to be some question of when a field action is or is not a recall. I guess it goes into a request for clarification of when to submit an 806 report and when the action described in the 806 is considered a recall and what other type of categories can 806 reports fall under.

MR. WALKER: So good morning, everyone.

So when the manufacturer or importer initiates a correction or a removal that addresses -- well, is initiated to reduce the risks to health proposed by the device, or is to remedy a violation of the act caused when a device may present a risk to health, unless that information is provided in the MDR, however, Form 3500A does not request all of the required information. And so I would stay away from submitting 806 information through an MDR report.

In terms of submitting that 806 report outside of a recall, a Class I, Class II or Class III recall, a report may be considered to be a market withdrawal, which is a situation where there's a minor violation and the product really doesn't create that -- major risk to health. An example is say you have older technology and the company or the firm no longer wants to support that technology, there isn't a risk with the device, it's just no longer being supported, so that would be a market withdrawal.

Another option is stock recovery. So that's when the product is in the direct control or ownership of the manufacturer, however, they're still doing some type of correction to the device. Examples for a stock recovery is if they send a lot of gloves to one of their own

warehouses and they may want to change anything, their labeling or something like that, that's doing a correction but again, that doesn't leave the ownership of the manufacturer.

So market withdrawals, stock recovery. There also may be a slight chance of a device enhancement, so Part 806 doesn't define a use term enhancement. But as one of the exemptions, it does mention the actions taken to improve the performance or the quality of the device. So if it's a device enhancement and the manufacturer can prove or justify that it improves the quality or performance of the device without a violation, it would be exempt from the 806 report. And so those are some of the things outside of a recall if the 806 report is submitted.

MS. MATTHEWS: And James, this is Stephanie Matthews. I completely agree and I think, in addition -- obviously, if it is exempt and certainly, following 806.20, I think we both noted in our presentations today, right, essential documentation still applies. So again, even as a manufacturer, ensuring all records are available whether it's reported to the FDA or not, if it's under those areas and in consideration even under the market withdrawal guidance and certainly those principles, both documentation, communication, reconciliation, all apply certainly at a manufacturer level in terms of records.

And our part of -- I'm sure this team is aware, you know, in terms of any type of audit and/or monitoring of the process that we continue to follow that guidance, from report-ability and all the way through closure, whether you're following 806.10 or 806.20 guidance.

So completely agree with -- in your respect and as a manufacturer, it is not uncommon that at times we reach out to FDA and talk through a situation to kind of walk through it if it's especially under -- likely in a Class III situation, around report-ability if it's something that's not a significant violation and your product may not have gone through U.S. commerce, I think there's some great discussions but I know, as a manufacturer, we've

had with FDA, to talk about consistency on that reportability. So I think the guidance from you and certainly, as a manufacturer, there's always an opportunity to collaborate and talk through the situation with the Agency.

MR. WALKER: Yeah, one thing I've learned being with the Agency roughly around 20 years now, is when firms come in or manufacturers come in for questions, a lot of times there's not a straight "we could give you a direct answer." It depends, right?

MS. MATTHEWS: Right.

MR. WALKER: Because every situation is unique and so we will work together to actually go through the regulations and identify the appropriate regulatory path.

MS. MATTHEWS: Um-hum.

DR. BRADDON: On that point of getting feedback from FDA, one of the presenters talked about design changes and if you have a question on whether it's truly a 510(k) or it's an internal documentation type thing, that FDA can review that. What is the pathway for reviewing that and tie that into -- one of the presenters said if you're doing an updated 510(k), like with design changes, that should be considered in -- whether the impacted products need to be recalled. So how do we get that feedback and how do we consider an updated 510(k) in a recall sense?

MR. WALKER: So once the 806 package is submitted, or prior to the 806 package is submitted, and the firm wants to just gather some information around their actions, that new 510(k) may be how they address the risks to health. And so it's hard to say that -- you know, you take a look at that guidance and you make a decision well, now we think this is a recall/we think this isn't a recall. As a part of that recall strategy, you need to take a phased approach. First, you're notifying the customers of the situation, then you may want to come in with that new 510(k). However, with the new 510(k) there's not a quick turnaround, right, and so you submit that 510(k) and it's a 90-day window there.

And so with that recall strategy, we just work with the firm to identify the steps that are in place to (1) keep the customer notified, and also reduce that risk to health in the meantime until that new 510(k) or until that updated product is available on the market to reduce that risk or to remove the risk or mitigate the risk.

MR. GOMES: But I think, Nick, there was also a question about how to document that decision. Would you recommend that companies conduct an HHE?

MR. WALKER: So the regulation doesn't require manufacturers or firms to conduct an HHE. However, I think it's a good practice because in a situation where there's an inspection -- you know, investigating and they see something and it triggered them to go down that path, and with that proper rationale and justification, it's a new sticky situation. And so identifying or performing that HHE, getting that medical officer or clinical reviewer's assessment and include that in the rationale would be a great practice.

MR. GOMES: And I think on FDA's website there are guidance documents on deciding when to submit a 510(k) and also what page is describing the recall or 806 requirements in detail, so those two resources might be able to help to tie into the two different aspects of decision making.

MR. WALKER: And again, it goes back to please don't hesitate to contact FDA, we're here and always available to help. And a lot of times it goes back to "it depends," right? And so we just walk through that situation together.

DR. BRADDON: Yeah, I tell our clients the difference between submitting a 510(k) and getting formal feedback and a letter to file or non-filing justification that's done internally is with the 510(k) process, you 100% know FDA agrees with you. And so it was very interesting, to me, when one of the reviewers who spoke this morning said if you're on that fence and you don't -- it's not black and white, right, it's very gray -- there's an avenue to get the feedback. I'm very familiar with the guidance, but I'd be super interested in how

to get that feedback when it's a very gray area.

MR. GOMES: So my understanding is, Linda, you could utilize the Q-submission pathway or simply just reach out to one of us in OHT 6, if it relates to an OHT 6 product. I think that sometimes companies are hesitant to reach out to FDA but, in my experience, I've always picked up the phone and talked to them and helped them as much as possible. So I would highly recommend to utilize that path.

DR. BRADDON: Great, thank you. I am interested in the filings, like MDR filings, the two different kinds, one from a patient and one from a healthcare provider and whether there is like you said, a 50/50 split. Is it 25/75? Who reports more?

MS. RIOS: Oh, thank you for that. I have to say that when compared to voluntary reporting and mandatory reporters, mandatory reporters have the highest volume. In terms of user facilities and manufacturers, manufacturers submit a lot more reports, leaving user facilities accounting for less than 1% of reports.

Similarly, the voluntary reporting is also less than 1%, which is interesting because when it comes to the MDR review perspective, MDR reviewers really do pay attention to -- they do pay attention to all reports, but they do -- we have noted that voluntary reports, they provide a lot more context of the adverse event itself compared to the summarized version of the event description that a manufacturer report would provide.

So it's important for the MDR reviewer to see -- they value seeing the entire picture of the adverse events. Manufacturers will provide the results of the investigation versus when compared to the voluntary report. But in terms of the adverse event itself, the event description, we have a very low volume of voluntary reports and user facility reports.

MR. GOMES: So Michelle, since we're talking about voluntary reports, would you like to talk about -- we talked about, during the presentation, we talked about -- mostly about 3500A. Would you like to discuss 3500B and who can use it and why it might be

important for us to know about 3500B?

MS. RIOS: Yeah. So yes, so mandatory reporters, they are required to submit reports under certain circumstances and there is a mandatory reporting form that is used and, as it was noted in the overview presentation, the form that is required is the 3500A. We do have other versions available for adverse event reporting for the consumers and the 3500B is the consumer version of the 3500 form. So we do encourage consumers to submit device-associated events using the 3500B form.

As noted, we do have a small volume of reports. From those over two million reports that we receive every year, less than 1% of that is voluntary reports. We do want to hear from the consumer's perspective what the device-associated event is and, like I said, it does help, provides MDR reviewers more --

MR. SPEER: I'm going to have to interrupt here, folks, I'm sorry. We are out of time. I know we're just getting started in the group discussion. Linda, John, thank you so much for moderating this. We tried to do the Menti survey a few moments ago, I know Dr. Song had some audio difficulties.

Dr. Song, can you test your mike to make sure we're good?

DR. SONG: Yeah, thank you so much, Jon. Can you hear me?

MR. SPEER: All right. Yes. Yes, we can. So go ahead and take that away with the Menti survey and then after this, we'll break for lunch. So go ahead.

DR. SONG: Yeah, perfect. Thank you so much, everyone. So now we will start our Menti survey regarding the Medical Device Reporting (MDR). So let's start with the first question.

Our first question is: What do you see as the primary reason for entering "No Code Available" or "Adverse Event Without Identified Device or Use Problem"?

Since there will be a delay, so I'm going to give you about 1 minute to respond.

Wow, a lot of people choose not enough industry training regarding filling out the form. As Stephanie mentioned in today's presentation, if you're not sure, you can discuss with your management or you actually can also e-mail FDA, we will be very happy to help you. Okay, let's go to the next question, please.

The second question is: Do you have thresholds in place for initiating actions (such as investigations, CAPA) related to a single or multiple MDRs? And also feel free to send your full comments to the mailbox oht6-feedback@fda.hhs.gov. A lot of people choose yes. Great, thank you so much for feedback. Okay, so let's move on to the third question, please.

So the third question is: How often do your surveillance and product management teams discuss MDRs with sales representatives, user facilities, and/or surgeons?

I think we have biweekly and also every 6 months. Okay, thank you so much. Let's go to the next question, please.

So the next question is: How often does your firm obtain explanted devices as a result of an adverse event?

Sometimes and frequently. And never. Okay, thank you again for feedback. Okay, so let's move on to the next question.

So the next question is: Are you currently implementing systemic improvements to increase the quality of MDRs (such as obtain a larger percentage of explanted devices?

Wow. I see it's changing. No. Okay, great. That's the end of the Menti survey. Thank you again for your participation.

MR. SPEER: All right. Thank you, Ting.

I know we had to cut things a little bit short on the group discussion and I appreciate all of your flexibility with that, but before we wrap up Session 1, let me hand things over to John Gomes and Linda Braddon for, I guess, a couple-minute summary of that session. So

John and Linda.

DR. BRADDON: John, do you want to lead?

MR. GOMES: Yeah, sure. Yes. So unfortunately I'm having some issues with my video but yeah, I would like to thank all the panelists for their valuable feedback on the questions. And I would also like to thank the audience for joining us in this discussion and sending in all your great questions, and I hope that you'll join us for the next two remaining presentation sessions and the corresponding group discussions.

DR. BRADDON: From an industry standpoint, I was -- the take-home message for me that I will definitely send to my clients is that if we have a question, we're going to reach out even if it's in an informal way and maybe that's not the right way, but we'll reach out and we'll do it informally and then FDA will tell us if we need to do something more formal with a Q-sub or whatnot, but I really appreciate knowing that it's a very open door. Thank you.

MR. GOMES: Absolutely.

MR. SPEER: Thank you, John and Linda, and to all the panelists and the moderators and the presenters for Session 1.

We're now at a point where we're going to break for about an hour for lunch, so we're going to take that lunch break, come back at 12:30 p.m. Eastern Time, just about 1 hour from now, for Session 2. And a reminder, if you have questions, you can submit those during this time to oht6-feedback@fda.hhs.gov. Thank you.

(Whereupon, at 11:32 a.m. a lunch recess was taken.)

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

(12:30 p.m.)

MR. SPEER: All right, welcome back. Ready to start Session 2 and then eventually Session 3. So Session 2 will be covering topics related to post-approval studies and postmarket surveillance studies.

Let me introduce our next presentation, it is on post-approval studies or PAS and 522 studies overview and requirements, and the presenter is Dr. Carolina Alvarez-Garriga from FDA. Dr. Garriga is a medical epidemiologist for the Division of Restorative, Repair and Trauma Devices, Fracture Fixation Devices Team at FDA, and she started working at FDA in 2012 at the former Division of Epidemiology. Before joining FDA, she worked as a faculty member for the University of Nevada and for the Ponce Health Sciences University, teaching graduate courses in epidemiology and research methods for public health master's and doctoral students, as well as conducting epidemiology research. Dr. Alvarez-Garriga has a doctoral degree in public health with concentration in epidemiology from the University of North Texas, a medical doctor degree from the Central University of Venezuela, and completed a medical residency in epidemiology of infectious diseases at the University of Carabobo, Venezuela.

DR. ALVAREZ-GARRIGA: Good afternoon, my name is Carolina Alvarez-Garriga. I am a medical epidemiologist in the Restorative, Repair, Trauma and Fracture Fixation Devices Team in Division of Restorative, Repair and Trauma Devices within OHT 6, Office of Orthopedic Devices. Today I will be presenting an overview of post-approval and 522 postmarket surveillance studies.

The purpose of my presentation is to review the postmarket mandated studies programs, that is the post-approval studies and the postmarket surveillance under Section 522 of the Food, Drug, and Cosmetic Act. We'll cover the FDA authority to impose

mandated studies and we'll go over guidance documents. Then we'll discuss the core process for both post-approval studies and 522s, the component of a study protocol or plan, and we'll conclude with a brief overview of mandated studies that have been required for orthopedic devices.

The postmarket mandated studies are required when a higher degree of uncertainty can be accepted during premarket conditions to postmarket monitoring requirements in making benefit-risk determinations. The postmarket mandated studies are important tools to continue monitoring device performance, to the evaluation of safety and effectiveness, and can be addressed in two ways, post-approval studies and 522 studies.

FDA has the authority to impose post-approval studies as condition of approval for Class III devices under Section 513 of the Food, Drug, and Cosmetic Act, under which we will consider whether postmarket data collection or other conditions might be structured to permit approval subject to those conditions.

C.F.R. 21 for premarket approvals and for humanitarian device exceptions also states that post-approval studies can be imposed at time of approval to continue evaluation and reporting on the safety, effectiveness, probable benefit for humanitarian device exception, and reliability of the device for its intended use. As such, the FDA may require a post-approval study or studies at the time of premarket approval, Humanitarian Device Exemption, or product development protocol application, to help assure continued safety and effectiveness or continued probable benefit in case of a Humanitarian Device Exemption of the approved device.

CDRH should only seek a study as condition of approval if it's in accordance with the policies established by the two FDA guidances listed below, which lay out the following criteria:

- Long-term evaluation by extended follow-up of premarket cohorts;

- Leveraging the premarket cohort by extending the follow-up for long-term data to be obtained postmarket as a condition of approval;
- Benefit-risk question where data are not available otherwise, to address unanswered questions that are not necessary to demonstrate premarket reasonable assurance of device safety and effectiveness. This includes benefit-risk questions of short- or long-term performance, learning curve training, performance in specific subgroups or rare adverse events; and
- Nonclinical questions on laboratory, bench testing, animal testing or explant/failure analysis.

The FDA guidance document for post-approval studies was updated in 2009 and provides verification on the contents of post-approval study protocols, interim and final reports, definitions for study progress, and consequences of failing to comply with a post-approval study order.

This guidance document is intended to assist you if you are subject to post-approval study requirements imposed by an approval order, by providing procedural information, recommendations on the format, content, and review of post-approval submissions, and recommendations applicable to both clinical and nonclinical post-approval studies.

This guidance document also aims to increase the transparency of FDA's approach to post-approval study requirements to stakeholders. Transparency initiatives include posting the status of post-approval studies on FDA's website or presenting the status in public meetings of the advisory panel.

Now I will talk about 522 studies. Postmarket surveillance orders can be issued for Class II and III devices at the time of market authorization or any time thereafter. For the statutory guidance outlined in postmarket surveillance under Section 522 of the Federal Food, Drug, and Cosmetic Act, the device must meet one of the statutory criteria described

in the next slide. Surveillance is up to 36 months. However, FDA may order longer surveillance if the device is suspected to have significant use in pediatrics.

Under Section 616 of the FDA Safety Innovation Act, 522 orders was further amended by specifying the orders can be issued at the time of clearance or approval and the device surveillance must commence within 15 months of order issuance.

FDA has also -- to order postmarket surveillance for Class II and III medical devices that meet any of the below statutory criteria. The first criterion is that a failure of the device will be reasonably likely to have a serious adverse health consequence. The second criterion is expected to have significant use in the pediatric population. The third criterion is whenever the device is intended to be implanted in the body for more than 1 year. And the last and fourth criterion is when the device is intended to be a life-supporting device used outside of a user facility.

Some examples of situations that may raise postmarket surveillance need are:

- Confirming the nature, severity, or frequency of suspected problems reported in adverse event reports or in published literature;
- Obtaining more experience with a change from hospital use to use at home or other environment or with a broader patient population than those studied in the premarket clinical trials;
- Addressing long-term performance of implantable and non-implantable devices, and assessing potential association between a device and adverse event once the device is on the market; for example, detecting unexpected or unexplained serious adverse events, setting changes in the nature of serious adverse events, and increase in the cumulative incidence rate of serious adverse events.

The FDA guidance document for postmarket surveillance under Section 522 was

issued in 2016 and provides stratification of the pre-522 process and expectation for content of surveillance plan, the reporting of consequences for not addressing an order, as well as stratification of the progress established definitions.

This diagram shows the core process for the post-approval study program and the 522 program. The process begins when the need for a post-approval study or a 522 study is identified. Then the orders are issued. The protocols or plans are developed. Please note that some post-approval studies have the full protocols developed by the time of device approval. When the protocols or plans are approved, we post the descriptions of the studies on the public web pages of the programs.

The studies commence when FDA approves the protocols or plan. They usually have a 6-month reporting schedule during the first 2 years and annually thereafter or as otherwise specified in the order. The web page will update the device's performance and progress status from the interim and final reports.

When the studies are finished and the postmarket requirements are addressed, CDRH should proceed to posting on the web the study's final results, updating the label and/or sending an FDA communication.

These are the components for a protocol or a study plan. They should include background and device description, study design, study population, study endpoints, sample size calculations and assumptions, and a statistical analysis plan.

To increase public transparency and keep all of our stakeholders informed of the progress of postmarket mandated studies, CDRH has established the post-approval studies and 522 postmarket surveillance studies databases. These databases are regularly updated with any new or revised information on study protocol parameters or study status or information related to the review of data from interim and final reports.

If the postmarket mandated studies are not progressing well, CDRH has the

authorization of potential regulatory actions, such as failure to comply with post-approval studies required as condition of approval constitutes grounds for withdrawal of device approval, and introduction or delivery or introduction into interstate commerce of a device that is not in compliance with its conditions of approval is a violation of the law.

Failure to comply with a postmarket surveillance order is a prohibited act under Section 301(q)(1)(C). If not compliant with a 522 order, a device can be considered misbranded.

This presents the overall status for post-approval studies imposed as condition of approval for orthopedic devices. On the next slide you see the status for all requirements, where 32% have been closed as completed. If we look at device type that includes active requirements, 76% are progressing adequately as of May 17, 2021 with only four in the progress inadequate category.

These present the reasons for the four post-approval studies in the progress inadequate category. And these are mostly related to reaching enrollment milestones and inability to maintain proper follow-up.

To conclude, post-approval studies and postmarket surveillance under Section 522 are important tools for device monitoring in the postmarket phase of total product life cycle.

Implementing studies can be challenging because of time required to develop protocols or plans, enrollment of sites and study subjects, and/or maintaining proper follow-up.

The best practices will be discussed in the next presentation.

Here is a list of important resources that we encourage you to review, including the two draft guidance documents for post-approval studies and 522 studies that CDRH posted on the FDA web page on May 26, 2021. The draft guidances are open to comment for 60

days. So, to assure that the FDA considers your comment on a draft guidance before CDRH begins working on the final version, please submit either online or written comments before the close date on July 26, 2021.

This concludes my presentation. Thank you for listening.

MR. SPEER: All right. Thank you, Carolina.

Again, folks, a reminder. If you have questions and comments throughout the rest of the sessions and presentations today, I encourage you to submit those via e-mail. That e-mail address is oht6-feedback@fda.hhs.gov.

Let's move on to our next presentation, and it will be on PAS and 522 studies best practices. Our presenter is Hongying Jiang from FDA. Helen Jiang has been serving as the safety signal manager within the Office of Health Technology 6, the Office of Orthopedic Devices at FDA since September 2020. Dr. Jiang was an epidemiologist at FDA from 2011 through 2016 and a lead epidemiologist and team lead of the Division of Clinical Science and Quality within the Office of Clinical Evidence and Analysis since 2016. Dr. Jiang has also been acting regulatory project manager and acting assistant director in OCEA and in the Office of Strategic Partnerships and Technology Innovation during 2019 and 2020.

She received her Ph.D. from the Michigan State University and worked as a bioinformatician -- and that's a word I haven't passed in a while -- and staff scientist at Michigan Technological University. She also served as the lead associate investigator at the National Institute of Allergy and Infectious Diseases at NIH from 2004 to 2011. Dr. Jiang has 18-plus years of multidisciplinary experience in biology, bioinformatics, and biomedical science, and she is an expert at both premarket and postmarket reviews, regulatory research, systematic literature reviews, safety signal management, and leveraging real-world evidence to ensure medical devices safety and effectiveness.

Dr. Jiang.

DR. JIANG: Good afternoon, everyone. My name is Hongying Jiang, a health scientist, former epidemiologist, and current safety signal manager in OHT 6, the Office of Orthopedic Devices.

Today I would like to share some examples of mandated studies in orthopedic devices. Thank you to our reviewers who have provided this to me. For each example, I'm going to introduce the background/issues first. Then provide our recommendations on do's and don'ts. At the end, I'll recap the takeaways of those examples.

Before we dive into each example, I would recommend that you think about the three key questions. First, what are the common issues in the mandated studies? Second, how do sponsors deal with this? Third, what could be improved?

Let's look at a report from GAO, Government Accountability Office, that surveyed 313 PASs and 392 postmarket surveillance studies to see the big picture on CDRH mandated study program. First, keep in mind that the data is relatively old. The PASs were those orders since January 2007 to February 2015, and postmarket surveillance studies, 522 studies, ordered since May 2008 to February 2015.

In all PASs, ortho devices was the second most common subjects and the top one in all 522 studies as of 2015. In the report, they also summarized that 19% of ongoing PASs have inadequate progress or otherwise delayed. Therefore, today we would like to discuss do's and don'ts.

Per GAO's report, a key reason for a study's delay may be limited patient enrollment in the post-approval study. There are other common reasons such as high loss to follow-up, progress inadequate, study population issues, study design changes, delayed analysis and reporting. In the following slides I'm going to provide one or two examples for each category, although there could be more than one reason for each study delay.

The second example is about a high loss to follow-up in the PAS at later time points,

especially after 5 years. The original IDE study only consented patients for 5 years follow-up and many patients were lost during PMA approval and the transition to the longer-term study. Some measures were taken to mitigate the biases, such as contacting patients, incentivizing them to return to the study; however, they were not very successful. This made the final PAS report and the subsequent labeling update less informative.

The best practice we would recommend is to ensure patients were consented for a longer-term PAS ahead of time, employ additional efforts to encourage every patient's follow-up visits, and analyze the PAS final results as much as possible, considering the missing data.

One advice is don't let the perfect be the enemy of the good or exclude some patients' partial data. Please make sure the labeling reflects the true long-term performance and clearly state the limitations of the study in a final report. Also, as a caution, and due to the lack of follow-up of some patients, long-term use of the device may be limited in removing certain warnings and precautions in the approved labeling.

Here I've included a slide to show how the follow-up rate should be calculated. It seems simple; however, you may be surprised to see that it hasn't been used consistently across different studies. To ensure consistencies, FDA has issued a guidance document, Clinical Data for Orthopedic Device Applications. It particularly included a patient accounting table shell, Table 2.

The actual completed subjects, Actual$^{A}$, is defined as patients with complete data for each endpoint, evaluated per protocol in the window time frame, and Actual$^{B}$ is defined as patients with any follow-up data viewed or evaluated by investigator, a.k.a. all evaluated accounting. Then two follow-up rates should be provided separately according to the two counts of the actual subjects.

So lessons learned from the above. Please report actual completed subjects per the

guidance. If you would like to report any additional modified actual count, please add another row to provide as additional calculations with a scientific and statistical rationale as to how the additional calculation supports the PAS study objectives.

Please don't modify the definition or use your own without any justifications, which may lead to over or underestimated follow-up rates.

The third example is about one study with inadequate progress for several years. Long story short, 8 years of the PMA approval, there were only less than 10 subjects enrolled. The study was designed to evaluate the effectiveness of the device under real-world use and to assess a clinical incidence with a control arm. There have been several protocol changes with the intention of improving enrollment such as reducing the requirement for imaging and loosening inclusion criteria. However, the sponsor has not met the proposed study timeline, to date, in either of the study arms. Finally, 8 years into the study, FDA requested the sponsor to add a warning to the labeling related to the unknown delayed safety and effectiveness relative to the comparator.

For this case, we recommend the sponsor to discuss delays in enrollment early and often with the FDA to try to address it as soon as possible. I can't emphasize how important it is, that please communicate early and often with us to mitigate any shortfalls and to ensure the inclusion/exclusion criteria and follow-up are as relevant to clinical use of the device as possible so that sites and subjects are willing to be involved.

Don't have many study protocol changes, as each major change must be approved by the FDA and the IRB prior to the implementation, and a series of agreement consent processes.

The fourth example is about a study population. This 522 study was ordered from a safety signal and designed for the on-label population. However, there was a large amount of known off-label use for this 510(k) device and thus, the enrolled subjects included both

on- and off-label populations that were not easily distinguishable. Also the off-label can drown out the on-label use.

Therefore, we would recommend considering the patient population for the on-label use only and make sure it's an easily identified population without or with minimal confounding factors or consider other study designs or leverage real-world data. More in the next presentation.

Of note, please do not use the 522 path to replace the IDE pathway for off-label use of the marketed devices.

As you've seen in the previous examples, study protocol could change in the middle of the study. The fifth example is an HDE study. The sponsor originally proposed to use a traditional PAS but later partnered the study with an existing registry for data collection following HDE approval. However, it was not communicated in advance to the review team, so the FDA review team approved the PAS protocol at the time of the HDE approval and soon after that, they had to review and approve the revised protocol.

Lessons learned from this example is that please discuss study design or any changes, your Plan B, ahead of time with the FDA team to determine the appropriate pathway, such as registries over a traditional clinical study, and resolve any differences in a timely manner.

Please do not send submissions without consulting FDA on the regulatory pathway. For example, some PAS study changes can be made in annual reports versus some must be submitted as supplements.

The last example is not a single example. Rather, it's about the unexpected changes due to unanticipated public health emergency such as the COVID-19 pandemic. During the pandemic, many clinical trials were affected, for example, study protocol deviations and changes, patients do not want to do in-person visit, or orthopedic surgeries were

considered elective.

FDA recognized the challenges and has taken actions promptly. So we strongly recommend you, please check FDA's official website for guidance. For example, FDA issued the "Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health" in March 2020 and recently updated on January 27th, 2021. At the end of the guidance there are many questions and answers. There are other guidance documents also issued by different centers of the FDA for specific product areas. If you don't find your questions there, please contact the FDA team.

Please do not implement any changes you're not sure about or without FDA's clear instruction. For example, some study endpoints, such as radiographics and certain pain or function assessments, cannot be conducted at home through the telemedicine.

Finally, let's recap what we've learned from these examples. First, communication is the key. To communicate timely and effectively is a common goal for all of us. Some can be done through e-mail, but some complicated issues may be better explained by a phone call, especially when discussing numbers and figures.

Secondly, make good use of informational meetings, Q-submissions, and interactive reviews.

Thirdly, please consider leveraging real-world data and real-world evidence, which will be further elaborated in our next presentation by Dr. Lilling.

Here are some guidance documents for your reference. All of them have included either some examples, Q&As, or checklists. Please check them out.

Thank you for your attention. This ends my presentation.

MR. SPEER: Thank you so much, Helen.

Let's move on to our next presentation and, as Helen mentioned, it is about real-world evidence case studies and it will be presented by Dr. Victoria Lilling from FDA.

Victoria Lilling is a native of Silver Spring, Maryland. She has served as a medical officer for FDA for 5 years. Dr. Lilling attended the University of Maryland in College Park where she earned a bachelor of science degree in physiology, one in neurobiology, graduating cum laude. She was inducted into the Phi Beta Kappa National Honor Society and Omicron Delta Kappa Leadership Honor Society and won a research scholarship from the prestigious Howard Hughes Medical Institute. Dr. Lilling completed her doctor of medicine degree at the State University of New York, Buffalo School of Medicine, where she was inducted into the prestigious Alpha Omega Alpha Medical Society and graduate magna cum laude, second in her class.

Dr. Lilling developed her interest in treating pathology and injuries to the shoulder, elbow, hand, and wrist during an internship and residency in orthopedic surgery at State. Dr. Lilling continued her education with a fellowship in microsurgery, hand, and upper extremity at Rutgers University in Newark, New Jersey, and then shoulder and elbow surgery at Johns Hopkins University Hospital. Finally, Dr. Lilling furthered her surgical skills in shoulder arthroplasty and arthroscopy with a fellowship in France under world-renown surgeon Dr. Laurent Lafosse. Dr. Lilling is a practicing orthopedic surgeon specializing in microsurgery, hand, and upper extremity surgery in Potomac, Maryland.

DR. LILLING: Good afternoon, my name is Victoria Lilling and I'm a medical officer in the Office of Health Technology 6, Office of Orthopedic Devices. I will be talking to you about the use of real-world evidence to support regulatory decision making for medical devices, specifically orthopedic devices. I will start with an overview of real-world evidence and then I will discuss case examples.

The purpose of this talk is to (1) provide a refresher on the overview of real-world data and real-world evidence; (2) present examples of how real-world evidence has been used; and lastly, to inform you of available review resources for real-world evidence. I will

start by discussing real-world data and evidence definitions and background. We will begin with how real-world evidence is used in regulatory decisions.

This chart is an overview of how real-world data can be incorporated into the traditional regulatory pathway, such as hypothesis generation or device innovation for IDEs or preclinical testing stage. Further into the pathway, we can use real-world data and evidence for premarket applications. And finally, the real-world data can be used for postmarket surveillance and post-approval studies.

So how do we turn real-world data into evidence? The data is collected from a variety of sources. Then this data is analyzed and the evidence is derived from the analysis of this data. In other words, real-world data is the collection of routine patient data. When it is analyzed to inform or make conclusions about a medical device, it becomes real-world evidence.

An analysis of this real-world data may consist of determining the suitability of the starting data by assessing its relevance and reliability, statistical testing of a captured clinical outcome against a performance goal, and presentation of this evaluation to support a regulatory submission. There are many considerations along this process and it requires a thoughtful study design to ensure that the resulting real-world evidence is appropriate for regulatory decision making.

Regarding valid scientific evidence, this is defined in 21 C.F.R. 860.7(c)(1). The key aspect of this regulation is that the manufacturer may submit any form of evidence to the FDA in an attempt to substantiate the safety and effectiveness of the device and the Agency relies upon only valid scientific evidence to determine whether there is a reasonable assurance that the device is safe and effective.

Equally, Subpart (c)(1) also notes that the Agency will determine whether the evidence submitted or available to the FDA is valid scientific evidence for the purposes of

determining the safety and effectiveness of a particular device and whether the available evidence, when taken as a whole, is adequate.

Here we can see what is considered valid scientific evidence. It can include:

- Well-controlled investigations;
- Partially controlled or uncontrolled studies;
- Well-documented case histories; and
- Significant human experience with a marketed device.

On the other hand, what is not acceptable is defined in 21 C.F.R. 860.7(c)(2):

- Isolated case reports which do not have sufficient detail to allow for determination of reasonable assurance of safety and effectiveness of a device;
- Random experience;
- Reports lacking sufficient details to permit scientific evaluation; and
- Unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.

Such information may be considered in the overall decision with other data; however, these sources cannot stand alone to determine safety and effectiveness.

Now, turning to the guidance document for real-world evidence to support regulatory decision making for medical devices. We will discuss relevance and reliability, which are defined within the guidance document.

Relevance of real-world data is assessed by evaluating several factors to determine if the data adequately addresses the regulatory question or requirement in part or in whole. It is very important to remember that real-world data sources are developed for non-regulatory purposes, for example, to document care in the case of electronic heath records or to submit insurance claims for reimbursement and claims databases.

The FDA will assess whether the individual data elements contained within an

existing data source is sufficient to be used for regulatory purposes. Most importantly, real-world data should apply to the question at hand. The data must be amenable to sound clinical and statistical analysis. Real-world data and real-world evidence are understandable using informed clinical and scientific judgment. The data must be properly analyzed and turned into valid scientific evidence before it can be used for regulatory decisions.

Factors to consider when evaluating the relevance of the data are :

- The representative population is generalizable to the relevant population for the device;
- The data source is used regionally, nationally, and/or internationally;
- How well the data source reflects the patient population's experience;
- The data source study design should be appropriate to address the regulatory question; and finally
- The data source should adequately capture patient medical history and preexisting conditions.

Now, turning to the reliability of real-world data. Reliability includes factors related to overall data quality. Real-world data reliability is assessed using characteristics of data accrual. Aspects of data collection to consider are the following:

- Pre-specification of the data elements to be collected;
- Unambiguous data element definitions;
- Structured data formats for data element populations;
- Method for data aggregation and documentation; and finally,
- Time frame for data element collection.

Data assurance and quality includes reviewing for quality of data element population, adherence to source verification procedures, and completeness of the data and finally, data consistency across sites and over time.

Key elements to consider in reliability are data sources and technical data capture methods, patient selection to maximize real-world population representation and to minimize bias, as well as patient protections.

Now, after adequately vetting the proposed real-world data to be used as evidence using relevance and reliability criteria that we just discussed, we can look for examples for use of evidence obtained. There are many potential regulatory uses for real-world evidence in the total product life cycle. Particularly focusing on postmarket uses which include, but are not limited to, real-world data infrastructures can serve as a framework for data collection and can be leveraged for post-approval studies. Real-world evidence can be used to identify safety signals for medical devices. And lastly, evidence from postmarket setting can support indication for use expansions and future device innovation, which is one way the total product life cycle comes full circle.

Next, I will discuss some examples of sources of real-world evidence that are commonly used to support regulatory decisions.

There are many sources of real-world data that can be leveraged for regulatory decisions. Here are some examples of real-world data sources:

- Electronic health records
- Claims and billing activities
- Product and disease registries
- Patient-generated data, including in-home use settings
- Data gathered from other sources that can inform on health status, such as mobile devices and reported events from device manufacturers, importers, device user facilities, and device users

Some of the expected benefits from the use of real-world evidence include:

- More efficient data collection

- Reduced cost
- Novel devices becoming available to patients more quickly

Also, real-world evidence can provide a better reflection of real-world device performance as it facilitates collection of outcomes which are not always feasible in traditional trials. This includes device performance in diverse patient populations and subgroups, as well as longer-term outcomes.

Overall, it is envisioned that the use of real-world evidence will reduce regulatory burdens and better meet the needs for public health and innovation.

CDRH recently published, in 2021, selected examples highlighting examples of real-world evidence used in medical device regulatory decisions. I will briefly describe orthopedic device examples which are highlighted in this publication.

The Hintermann Series H3 Total Ankle Replacement System, which is indicated for the use as a non-cemented implant to replace a painful arthritic joint due to primary arthritis, post-traumatic arthritis, or arthritis that can carry to inflammatory disease. The H3 system has been commercially available in Europe since 2003. Real-world evidence sources considered in this submission were outside the U.S. or OUS registry data, performance goals derived from a meta-analysis that included published literature and safety data. Real-world evidence was used in both the premarket and postmarket submissions. The premarket submission real-world evidence was used as the primary source of clinical evidence. For the postmarket submission, the post-approval study consisted of longer-term follow-up in OUS registry.

The next example is The Tether - Vertebral Body Tethering System, which is indicated for skeletally immature patients that require surgical treatment to obtain and maintain correction of progressive idiopathic scoliosis with a major Cobb angle of 30 to 65 degrees, whose osseous structure is dimensionally adequate to accommodate screw

fixation as determined by radiographic imaging. Patients should have failed bracing and/or be intolerant to brace wear. HDE approval was based on a single-center, nonrandomized clinical study under IDE application G150001 in 57 subjects, 47.4% of whom reached skeletal maturity by the time of the database lock. Real-world evidence was collected from retrospective review of medical records. A post-approval study embedded within a patient registry was utilized to mitigate uncertainties related to probable benefits of the device for longer-term prevention of spinal curve progression and avoidance of spinal fusion, as some patients were still growing and remained at risk for curve progression. Use of real-world evidence collected in a post-approval registry allowed CDRH to balance premarket and postmarket data collection requirements and facilitate timely patient access to this important new technology without undermining patient safety.

The next example is the Ceramax Ceramic Total Hip System, which is indicated for non-cemented use in skeletally mature individuals undergoing primary total hip replacement surgery for rehabilitation of hips damaged as a result of non-inflammatory degenerative joint disease or any of its composite diagnoses of osteoarthritis, avascular necrosis, and post-traumatic arthritis. Primary clinical data consisted of prospective, multicenter, single-blind, controlled clinical study which included 264 subjects. The United Kingdom and Australian National Joint Registry data was leveraged for postmarket evaluation in addition to a long-term follow-up of previously enrolled subjects and a cohort of new enrollment subjects.

And finally, the last example is the activL Artificial Disc, which is indicated for reconstruction of the disc at one level, L4/L5 or L5/S1, following single-level discectomy in skeletally mature patients with symptomatic degenerative disc disease with no more than Grade 1 spondylolisthesis at the involved level. The activL Artificial Disc is implanted using an anterior retroperitoneal approach. PMA approval was based on a prospective,

multicenter, randomized controlled, non-inferiority clinical trial which included 324 subjects. In addition to conducting two long-term post-approval clinical studies, the sponsor was required to provide data as part of the PMA annual report from an explant analysis retrieval study that will be conducted for 10 years and include clinical narratives, copies of operative reports from the original surgery, operative reports from subsequent surgeries and the explant surgery, pathology reports, and conduct an explant analysis. Note, the collection of explant retrieval data is identified as a condition of approval for other total disc replacement devices and is considered a type of real-world evidence.

Clinical evidence for devices comes in many forms across the total product life cycle, including real-world evidence.

Supporting evidence generation with relevant and reliable real-world evidence can facilitate timely access to safe and effective medical devices.

High-quality real-world data sources are strategically positioned to further enhance the care of patients and device safety and effectiveness.

Real-world evidence plays a very important role in premarket and postmarket device evaluation and surveillance.

Thank you.

MR. SPEER: Okay. Thank you, Dr. Lilling.

And let's move on to our next presenter, and this comes from industry, and it's an industry perspective on PAS and 522 studies, and the presenter is Paul Coplan with Johnson & Johnson. Paul is the vice president of epidemiology and real-world data sciences for medical devices at Johnson & Johnson, leading a team of epidemiologists, data programmers and biostatisticians. Paul completed a B.S. honors in biochemistry and physiology at the University of Witwatersrand, and master's in public health and nutrition at the University of Massachusetts, Amherst, a doctor of science in epidemiology and

biostatistics at Harvard School of Public Health, and an M.B.A. at Wharton Business School at the University of Pennsylvania. Paul has been a pioneer in using epidemiology and real-world evidence to develop new vaccines, medicines, and medical technology and to assess postmarket safety and effectiveness. So let me hand it off to Paul.

DR. COPLAN: Good afternoon. My name is Paul Coplan, I'm the vice president of epidemiology and real-world data sciences in Medical Devices at Johnson & Johnson. Thank you to the organizers for the opportunity to speak today and thank you for your attention. The topic of my presentation is implementing PAS and 522 studies, providing an industry perspective.

My disclosure is that I'm an employee of Johnson & Johnson, but the opinions expressed in this work are my own and not those of Johnson & Johnson.

I'll be talking on how PAS and 522 programs run within a company; difficulties in complying with most postmarket programs for PAS and 522 studies; examples from FDA's RWE examples document that was recently put out; addressing the relevance and reliability of RWE; what improvements can be made by FDA; and how can industry and the FDA work together to better these programs.

Firstly, how PAS and 522 studies are conducted depends on the research question and the best data source to address the best research question. If it's a new device with no registry or available RWE, then an IDE rollover clinical study is used and it would be done by a clinical team or clinical operations team. If there's a registry available for a commonly used implantable device such as a hip and knee replacement, one of the registries will be used and it would probably be a different group that will conduct the study.

We've also seen recently an example of a label extension where the label -- where there was extensive use of the product for the intended indication available in electronic health record databases, and even though the label extension itself was based off an IDE

study, the PAS study used an electronic health record database and this was in the Office of Health Technology 2 for a cardiovascular product. And this would be done by a different team.

So what are the difficulties in complying with a PAS or 522 study program? Firstly, difficulties in enrollment. One of the things that we've seen is the market can move towards product configurations identified or perceived to perform better, so surgeons won't use that particular construct. For example, in a study of a hip replacement device implant with smaller hips and larger hips, there was a move towards larger hips by surgeons because it was perceived to have certain advantages, whereas making the use of smaller femoral hips is very rarely used. Therefore, it turned out to be very difficult to enroll study subjects in the PAS for smaller femoral hips.

There's also difficulties in retention. Longer-term follow-up is difficult to achieve in IDE rollover studies or company sponsored registry studies, particularly 5- or 10-year follow-up visits and particularly for patients who have no problems to come back for 6, 7, 8, 9 years is burdensome.

The other thing is that patients move away from the clinical study site. For example, they may retire and move to Florida, so it's very difficult for them to come back to their original study site for a follow-up visit.

It turns out to be easier to achieve 5- or 10-year follow-up in registries that are able to link the registry to other mechanisms of following up patients, so particularly in countries where there's cradle-to-grave follow-up systems, such as Sweden or the UK, and these X years registries can thereby achieve easier 5- to 10-year follow-up.

There are also barriers to using such data as part of PAS studies. There's a desire by the FDA that the sponsor demonstrates matching of patient progression and device usage between the OUS registry population and the U.S. population, for example, if there were

similar stages of osteoarthritis pathway.

Another issue is the barriers to using electronic health record or hospital administration databases where the onus is on the sponsor to demonstrate the reliability and relevance of RWE. And I'll talk about that a little bit further.

So an example in the FDA document that we just heard about is, was the use of an orthopedic example for a PAS study using an OUS registry. This was for the Ceramax ceramic-on-ceramic hip replacement. It was approved by an IDE using a PMA approval with a PAS requiring a condition of approval.

Now a little bit about that PAS study. The PAS study included two constructs, the 28 mm femoral hip, the smaller hip and the bigger hip, and the primary endpoint was either 5 years or 10 years. And for the 36 femoral hip there were three studies, the last one used joint registry data from the England and Wales National Joint Registry and the Australian Orthopaedic Association National Joint Replacement Registry.

So what we can see from this is PAS studies were designed for each configuration of the device, and the OUS registry data was accepted as part of the third PAS to provide supplemental information to the IDE rollover and newly enrolled subjects components of the data.

So addressing the relevance and reliability of RWE, this is a long topic and the FDA has a great guidance on this, put out in 2017. But I wanted to provide one recent example from a NEST test case. This was a test case for an intervertebral body implant or IVBI using electronic health record database. The study used the delta method to compare the treatment IVBI with a comparator IVBI and this type of study could be used for a PAS study.

So the goals were to test the feasibility of conducting a PAS study of a lumbar IVBI and to apply surveillance tools such as the delta method to evaluate IVBI device safety. The study was conducted by Lahey Health System using the data warehouse of Lahey. Lahey is a

five-hospital network in eastern Massachusetts. They use Epic EHR in all the five hospitals for all inpatient and outpatient clinic activities. They have records of over 3.4 million distinct individuals and in addition, they collect PROs and radiographs for all spine surgeries at set time points.

The study endpoints were the proportion of patients undergoing any spinal reoperation within 12 months at the time, and the secondary endpoints at the time of surgery and need for blood transfusion, and it was 12 months since surgery, mortality, hospitalization for surgical site infection, and any repeat hospitalization. The comparator was a comparator IVBI. We used propensity score matching and weighting to adjust for confounders. We also included a negative control which provided an outcome unrelated to spine surgery to assess if there was residual confounding between the two groups.

These are the results for the primary and secondary endpoints. The p-value shows there was no significant difference between the treatment IVBI and the comparison IVBI, 424 subjects, matched subjects in each group. So overall, the conclusion of the report was there was no signal detected in the outcomes with a 0.05 significance level. So this is one example of how PAS studies could be done using electronic health records database.

Now, what improvements can be made by FDA? Well, PAS studies are designed with good scientific principles at the point of product approval, but they may not be feasible to implement because, as we've mentioned, there's preference for data on each device configuration which may or may not account for shifts in the preference for the different configurations of a device, and also the length of follow-up, which is very difficult to collect in a U.S. based standard clinical trial or registry.

It also would be a great improvement if FDA could adopt greater flexibility to use real-world data to reflect what's happening in the real world, such as more flexibility in accepting OUS national registry data for long-term follow-up and some of the things that

could be relaxed here is the FDA's desire to demonstrate comparability of populations, OUS and in the U.S., and also could RWE become the sole source of evidence rather than adjunctive to IDE continuation of patient enrollment in PAS. Registries are larger, more representative of general usage patterns, and also provide a more diverse surgeon experience level.

A further factor about real-world evidence is it -- for inclusion of racial and ethnic minority subgroups, it's much easier to represent those groups through real-world evidence data sources.

Another factor in the flexibility around using real-world evidence is real-world evidence which comes from a healthcare system's electronic health record databases where the data needs to be fit for purpose. And one of the things we've seen in identifying whether the data is fit for purpose, in other words, is it relevant and reliable as indicated in the FDA guidance, is a checklist where the data source has to meet every component of relevance and reliability.

And what could improve things greatly in terms of the adoption of this kind of data, which is a very rich source of data, widely available, but has been used very little to support regulatory decisions to date, is a risk-based assessment of real-world evidence reliability and relevance.

So what does a risk-based assessment mean? It is to evaluate for each of the components that are listed in RWE guidance, would that component have an impact on the results or not. And what that means is that, for example, if we're comparing two groups, say one IVBI against another IVBI, in the same real-world data source, if there is less than complete follow-up in both groups, well, in comparing the two groups there is equivalence between the groups because they both have that issue and so the question is whether there is differential follow-up in the one group versus the other that would bias the results when

comparing the two groups. So that reflects a risk-based assessment to understand is that particular factor -- would it influence the results or is it because it's the same in both groups, it wouldn't be a differential factor.

So in summary, the key points are the feasibility of the study and one consideration is could FDA consider an adaptability of PAS study design and as well as milestones that are based on market usage. In other words, if there's a certain amount of market usage, then those particular configuration milestones kick in, but if the market usage is too low, then perhaps the focus is on the other constructs where there's greater market usage.

And secondly, flexibility in accepting RWE. And one thing that would be interesting to consider is would the Office of Health Technology 6 consider an example of using an orthopedic PAS study using real-world evidence from a healthcare system's electronic health record database. Just as the Office of Health Technology 2 has adopted one for a cardiovascular product, would the orthopedics group consider trying one out and seeing how it works to advance the use of RWE to support regulatory decisions?

Thank you very much and I look forward to the questions and discussion.

MR. SPEER: Okay. Thank you, Paul.

We're going to move now to our next Menti survey and it's presented by Michael Owens from FDA. Michael joined FDA in 2007 as a collaborative reviewer, splitting time between what was then called the Office of Device Evaluation and the Office of Surveillance and Biometrics. In 2019 he became the assistant director within the Division of Joint Arthroplasty Devices with the primary responsibility of leading the shoulder team.

So Michael, I'll let you go ahead and start the Menti survey.

MR. OWENS: Thank you, Jon. And I hope everybody has enjoyed Session 2 as much as I have so far. I'm just going to go through a few questions that we drafted based on the content of the session and the talks that you just heard. I'll read each question in totality

and then allow for time due to the delay in this broadcast, as well as time to give answers.

So let's go ahead and get started. The first question is: Please briefly state what is the biggest challenge you have encountered while implementing a post-approval study or 522 study.

Earlier in the talks we saw enrollment, continued follow-up continues to be a challenge that we've observed. I'm curious to see what the audience thinks.

(Pause.)

MR. OWENS: I see some answers coming in. Thank you, everybody. Very interesting, very interesting. All right, I'm going to move on to our next question.

The next question is: Can you briefly state what you would do if you have a post-approval study or 522 study that is marked as "Progress Inadequate"?

I hope that communicating with the Agency is a part of your answer, as we always encourage that.

(Pause.)

MR. OWENS: All right, thank you very much for those that responded. For the sake of time, I'm going to move on to the last question.

And the last question is: Which real-world data source do you think will be most effective to produce viable real-world evidence for use in regulatory decision making?

(Pause.)

MR. OWENS: I see electronic health records coming in, yes, that was one that we saw as a part of Dr. Lilling's talk. Also the Agency is very, very involved in registry work. I see hospital data linked to Medicare data and EHRs. The FDA would be interested to hear who submitted that answer and what their thoughts are on that. A registry. As I mentioned, we're doing a lot of work in that space. And retrieval and explant analysis as well as literature. Again, all excellent data sources that we investigate routinely. I want to

thank everybody for participating in this Menti survey and I'm looking forward to a great group discussion.

MR. SPEER: Okay. Thank you so much, Michael.

And we are going to transition now to the group discussion. I want to remind the moderators and the panelists that we do have a limited amount of time, so brevity is important, but obviously we want to get into some of these topics.

Let me introduce the moderators. First, Nilsa Loyo-Berrios is a Ph.D. and she's with FDA, she's the deputy director in the Division of Clinical Science and Quality, Office of Clinical Evidence and Analysis in the Center for Devices and Radiological Health. She joined FDA in 2005 and worked as a regulatory epidemiology reviewer in the clinical areas of obstetrics and gynecology, cardiovascular, gastroenterology, urology, and respiratory medicine. She has extensive experience on the application of epidemiological principles, particularly on the observational methodologies and analyses to the evaluation and surveillance of medical devices through the total product life cycle. As deputy director, she provides oversight of methodologies development and analyses, infrastructure development, and partnerships and development and interpretation of policies for mandated studies, including PAS and 522 studies.

The other moderator is Russell Schenck with Zimmer Biomet. Dr. Schenck has almost 30 years of experience in all areas of planning, execution, analysis, and reporting on company sponsored clinical studies designed to gather evidence required for regulatory and business needs. He's currently responsible for global clinical strategy for Zimmer Biomet reconstructive and sports extremities and trauma businesses. Before joining industry, he resulted in or did work in clinical research design and statistical analysis at the University of Michigan, and a Ph.D. in evolutionary biology from Rutgers University. He held academic positions at UM and the College of William and Mary.

Now let me do a brief introduction of the panelists. Joining from FDA is Dr. Hong Cheng, he's the lead health scientist for the Office of Clinical Evidence and Analysis in CDRH at FDA. Dr. Cheng received his M.D. in 1982 from West China University of Medical Sciences, and his Ph.D. in epidemiology from the University of Alabama at Birmingham in 2000. Dr. Cheng joined FDA in 2008 as an epidemiologic reviewer in the Office of Surveillance and Biometrics. Before joining FDA, Dr. Cheng had worked in academia teaching students and conducting epidemiological research for more than 20 years.

Our next panelist is Dr. Veronica Sansing-Foster. She is an epidemiologist at FDA's Office of Surveillance and Epidemiology. She earned an honors B.A. in psychology from the University of Chicago in 1999, and earned her master's and Ph.D. in psychiatric epidemiology from the University of Pittsburgh Graduate School of Public Health in 2008 and 2010 respectively. Dr. Sansing-Foster began her career at FDA in 2010 and has been in both CDRH and CDER. Since 2019, she's currently worked as a senior epidemiologist in the Office of Clinical Evidence and Analysis at CDRH.

Also joining the group discussion are some of our earlier presenters: Dr. Helen Jiang, Dr. Carolina Alvarez-Garriga, and Dr. Paul Coplan.

So proceed, moderators, with the discussion.

DR. LOYO-BERRIOS: Thank you, Jon. I want to start by thanking the presenters for the great presentations that we just heard, and the panelists for staying with us and joining us for the great group discussions.

I wanted to start with a question to Dr. Carolina Alvarez-Garriga. Thank you for the overview of post-approval study and 522 program. You mentioned the Agency recently released two draft guidance documents with updates to the programs. Can you briefly describe what those updates are and what was the rationale behind those updates? And remind us of the public comment period and when it ends so we can provide valuable input

to the Agency.

DR. ALVAREZ-GARRIGA: Thank you, Nilsa.

Very briefly, because I know we have a very short time for our discussion. The updates for the draft guidances include the recommendations to help facilitate FDA's review of post-approval study protocols or 522 study in a timely manner. Also, the guidances include recommendations for study timelines including enrollment milestone and study completion. Revised definitions to post-approval study statutes -- for example, a study ongoing or delayed, is that progress adequate or inadequate, and including -- like well-designed -- as we believe that everyday progress of the post-approval study, and revised FDA review time goals for post-approval study submissions, talking about post-approval study -- very similar for 522 study draft guidance.

And the rationale for these updates is to minimize the challenges that have to be extensively described in the referent presentations for decision, to minimize the challenges implementing both market mandated studies including the time it can take to get agreement and approval of the study protocols in case of possible study or study plans for 522 studies. To also take into consideration slow enrollment of the study sites and subjects and they need proper follow-up rates. Some of the proposed update policies are intended to ensure these studies are initiated and completed -- and that the FDA review of the data from those studies is efficient.

Also important to highlight, as I mentioned in my presentation, these draft guidances include important documents, links to documents for other approved guidances that were not included in the guidance, in the documents from -- that were published a few years back. And the most important, the most important reminder is that the two draft guidances documents for post-approval study and 522 studies were posted on the FDA web page on May 26, 2021 and are open for 60 days for comments. So it is very important to ensure that

FDA considers your comments before CDRH begins working on the final version and that requires comments before the closing on July 26, 2021, which is the most important thing to remember.

DR. LOYO-BERRIOS: Thank you, Carolina.

So a reminder, people, go and read those guidance documents and provide feedback to the Agency.

So I'm going to let Russell then go over some of his questions.

DR. SCHENCK: Thank you, Nilsa, and thank you to the panel, particularly for this session. Very informative and very well organized and of great interest to myself, having been in industry for a long time.

A general question for the panel, FDA, and industry. As the demand for orthopedic procedures has expanded in recent years, many clinicians are no longer following their patients annually as part of their standard of care, right? These studies are therefore burdensome for investigators and patients. When we are required to do annual follow-ups involving clinic visits, they don't mirror real-world standards of clinical practice. Presuming acceptable follow-up compliance, is the Agency comfortable with post-approval study designs that don't require annual clinic visits?

And maybe a second part of that question, you know, in this digital era where telemedicine and remote patient monitoring are becoming increasingly part of our healthcare systems, are there wearable sensors and those sorts of technologies that could provide us with data that would be reliable and useful in post-approval settings? And I'll listen, thank you.

DR. SANSING-FOSTER: Thank you for asking that wonderful question. Now, while in-clinic visits still may be necessary for certain assessments in the post-approval studies, FDA is willing to engage in discussions with manufacturers on how they can incorporate

these virtual visits into their post-approval studies. Now, the beauty of the virtual visits, they can add the benefit of easier follow-up for patients who may not be able to make it to their in-person appointments. This may be especially important for patient-reported outcomes. For instance, instead of subjective reports of pain with physical activity as reported retrospectively by patients at the clinical visits, a wearable sensor in real time could record that physical activity plus the amount of pain associated with that particular activity.

So we are very open to discussions. So we don't see that in-clinic visits will be completely eliminated. We are definitely open to discussions with you when you start to design your post-approval studies.

DR. LOYO-BERRIOS: Thank you, Veronica.

So one of the aspects that we have been talking about is the flexibility in terms of changes to ongoing studies that are not progressing as expected and maybe, you know, due to changes in the market and how the devices are being used or not. One aspect of being able to do that is having availability of infrastructure that could serve -- you know, to provide that relevant and reliable data and evidence.

So I wanted to touch upon ongoing efforts, so if Dr. Hong Cheng can speak briefly about the ongoing ortho CRNs within the offices of NEST and MDEpiNet.

DR. CHENG: Sure, thank you. As we know now, NESTcc is well known actually as a coding research center and collaborative community. Also is a correlated network of orthopedic registries in the U.S.. Together with MDEpiNet, they all support using real-world data and real-world evidence for medical device evaluation.

Within the framework of NESTcc, there are some examples of projects well worth mentioning. First one to talking about the project for the establishment of or development of objective performance criteria for revisions and quality of life changes after -- as major

outcomes after hip and knee replacements. The use of OTC (ph.) in contrast to use of concurrence controls can help designing a study in a more efficient way, which may benefit stakeholders in terms of time and the cost.

The second example I'd like to mention is the linkage between ortho -- I mean, the ortho CRN and the state and bill code claims data, that way it can expand the capacity of registry, advance registry efforts, including validation of complications, increasing follow-up rate and follow-up events and allowing adjustment for confounding facts of comorbidities and may obtain more patients' characteristic information. These projects could be -- yeah.

(Cross-talk.)

DR. LOYO-BERRIOS: I'm sorry, Cheng, I don't mean to cut you off, but we're running out of time --

DR. CHENG: Sure.

DR. LOYO-BERRIOS: -- and I wanted to give some opportunities for the industry representative, Dr. Coplan, to speak a little bit more about what would you recommend to both the FDA and industry in terms of what can be done. I think we focused on reliability, which is important, but relevance is an aspect that we shouldn't forget and when we're using data from outside of the U.S., ensuring that data can be generalized to the U.S. population is very important. So can you speak to what we can do for both of us, industry as well as FDA, to ensure that we have both components, relevance as well as reliability?

DR. COPLAN: Thank you for that question. Yeah, it's a difficult one because oftentimes how the product is used is different in Europe and Australia to what it is in Europe. And in the U.S. So generally, the question would be whether the usage of the device is as it's used in the OUS registries which substantially influences the outcomes, particularly if we're looking at safety outcomes for the device as it's indicated in the U.S. So that requires somewhat of a risk-based assessment because real-world evidence doesn't

give us exactly what we need because it's used in the real world, as was mentioned earlier, and therefore there has to be some kind of risk-based assessment of whether that would substantially influence the outcomes. Thanks.

DR. SCHENCK: I have a question for our FDA staff here. I've been around a long time and I'm not sure if all of you have been around long enough to recall the -- almost 10 years ago, many of the large orthopedic companies were provided a Section 522 PMS order relating to metal hip articulations. This was a very difficult issue, a challenging issue. Some companies have satisfied that obligation in the interim 10 years and others remained marked as progress inadequate.

My questions are, you know, did FDA generally achieve its objectives with that particular Section 522 order in orthopedics? What were some of the key challenges and solutions? What worked, what didn't work? And then finally, is there a plan to further communicate what was learned on that particular 522 study, either through peer-reviewed publications or other kinds of FDA communications? Thank you, I'll listen.

DR. JIANG: Hi, this is Helen. I can take this question. Can you hear me clearly?

DR. SCHENCK: Yes.

DR. JIANG: Yeah, this is a very good question, Russell, and it's a challenging one. So to briefly answer your question as cognitive of the time, FDA has this topic website for posting the post-approval study and also the 522 studies, including their study designs and the final results. And for this particular case that you mentioned, metal-on-metal hip replacement, we have actually a new website designated for putting all of the information related to metal-on-metal, those hip replacement implants, okay. So in that, particularly, there is a -- I can share the link to the website and in that there is a particular section about all the FDA activities, including major -- like, four parts of the information. First is about the rule change, all of them need to be changed to be a PMA submission with clinical data and

secondly, we summarized the interim results for two types of studies, clinical study and the retrieval analysis from all of the 522 studies on the website, as well. Also, FDA has helped with the standards group to develop some new standards and we also have invested a lot in the research and publications besides some peer-reviewed articles -- other white papers or technical papers. So I think more information can be found at the website. Thank you.

DR. SCHENCK: Thank you, Dr. Jiang.

DR. LOYO-BERRIOS: Thank you to the panelists. I'm not sure how we're doing in terms of time, do we have time for some additional questions? Okay, so we have some time. I'm going to have another question for Helen and that is I know that it can take time to get agreement and approve the study protocols, so can you speak to examples of those specifics and how to communicate effectively and getting agreement to those protocols so they can be approved in a timely fashion and the studies can be started in a timely fashion?

DR. JIANG: Thank you, Nilsa, for that question. Yeah, some of those I already presented in the slide, that is, you know, FDA team is very open to work with the company interactively. You know, I like what Linda summarized at the end of the last session, is the bottom line is if you have anything that you're not sure about, you have a question about, come to the review team, you know, to work with us.

So in terms of communications, some people prefer like written e-mails, you know, we're not using the old-fashioned letters anymore, but it could also be phone calls or teleconferencing right now. So it depends on the needs of the question, how big is the question. You know, so I think there are different common senses about how to reach to FDA. So in general, you can imagine our reviewers are very busy with a lot of reviews in their queue, so you don't want to expect them to answer your call right away to make any decisions. Okay, so we normally would recommend you to send an e-mail first. If there are complicated issues with long histories or some numbers or figures you want to discuss,

more complicated issues, maybe setting up a teleconference would be better so that we can share a screen to understand better what's the problem and how to address them. So in general, our team is very flexible and we welcome different ways of communication and then keep in mind that, you know, give us reviewers some time to think about that decision, we may not be able to answer your questions right away.

DR. LOYO-BERRIOS: Thank you, Helen.

We heard from Dr. Lilling's presentation of several successful cases in which RWE was used for regulatory decisions. I know she's not joining us at the panel, but Dr. Sansing-Foster, can you maybe talk a little bit about what made those specific databases and the methodologies successful? Can you give us a little bit more details?

DR. SANSING-FOSTER: Sure, I can give you a brief overview of the details and it all goes back to the cornerstones of relevance and reliability, but we also have to consider the benefits.

Now, regarding relevance, Hintermann, Tether, and Ceramax, they leveraged preexisting patient registries which were real-world data sources that were designed for non-regulatory purposes.

Now let's look specifically, just for time's sake, at Hintermann and Ceramax and this actually all ties back to Dr. Coplan's presentations. They used preexisting outside-the-U.S. registries in Switzerland and the UK and Australia, and certain models of these devices had prior approval outside of the U.S., which means that they were able to get postmarket data at the time of approval and, in addition, outside-of-the-U.S. registries. And healthcare systems -- well, the healthcare systems specifically can follow a patient from cradle to the grave, so you have greater ability for long-term data. So that is a general overview of some of the things that made Hintermann and Ceramax very successful.

DR. LOYO-BERRIOS: Thank you. I'm looking at my notes here. So Helen or to the

FDA panelists and Paul, please chime in as you see you could, one of the challenges with the post-approval studies, you know, once the device is on the market patients can get access to the device who were not necessarily joining a post-approval study and investigators may not be as interested in doing any post-approval studies compared to premarket studies where new stuff or new technology is being evaluated. So can you share your thoughts around how to overcome those two challenges? Maybe start with Paul, just to get the industry perspective on that.

DR. COPLAN: I think that's one of the advantages of real-world evidence, because in real-world evidence you could capture the usage as it's occurring. You don't specifically have to enroll patients into a study, you could be studying them as usage is occurring. If it is enrollment in -- it requires patient enrollment or rollover from the IDE clinical study, then generally incentives have to be provided both to the clinician and to the patient. And generally, what we've found is some of the surgeons that are less likely to be participating in other studies would be more likely to participate in these studies as a way to kind of get involved in doing -- get started in doing clinical studies.

DR. LOYO-BERRIOS: Thank you, Russell (sic). That's really key, you know, for being able to use real-world evidence and I keep going back to the relevance aspect because I know reliability is very important, but when the reviewers are looking into a submission, the data needs to be relevant with regards to the request, the regulatory submission that is being requested, like the indications for use, the population and all that.

Any other comments from our FDA colleagues?

DR. COPLAN: If I could just add another quick comment there. You know, I think the guidance document is extremely helpful in determining and defining what's relevant and reliable. From an industry perspective, you're going to need like a recipe book on how to do real-world evidence and from that context, the guidance is actually quite hard to identify

like a checklist of what elements does the sponsor need in their real-world evidence. So one thing to consider is whether FDA, either through -- and perhaps through MDIC or some other kind of cross-collaboration forum or MDEpiNet, would consider creating a checklist for relevance and reliability and data quality, exactly what elements are needed, so that the sponsors can kind of work through that and it simplifies our job in producing evidence to document the relevance and reliability.

DR. SCHENCK: Thank you for that comment, Paul.

DR. LOYO-BERRIOS: Thank you, Paul.

DR. SCHENCK: As another industry representative, I think that would be very useful.

DR. LOYO-BERRIOS: Yeah, I agree. And I see Michael Reese (ph.) from the FDA nodding, so I think they agree, as well. So that's one good take-home message from this session is maybe having better clarity from the FDA side in terms of what is needed, you know, for regulatory decisions when it comes to the relevance and the reliability and having a checklist may be one option.

So I think we are nearly at the end of our time, so I'm going start with a summary. I think what I heard is that these studies are very important for the continued evaluation of the devices as they get to the market and to assess safety signals when it comes to the postmarket surveillance under Section 522. As such, they're very important and very important that they get started, initiated, and completed in a timely fashion.

Now in reality, there are challenges while implementing those studies and we, FDA, acknowledge those challenges, right? It can take time to approve a protocol or a plan and even when we have those approved in a timely fashion, then we can have problems with slow enrollment and then data quality, follow-up that is differential by the groups and so on and so forth. So we heard about flexibility once the devices get on the market, the need for flexibility, because the device may not be distributed or used as expected, in which case

there will be slow enrollment. And we heard about the examples where real-world has been successful for regulatory decisions.

So I thank you all for the great presentations and the great discussion. I'll let Russell do some summarizing from his side.

DR. SCHENCK: Yeah, I think you summarized well, Nilsa. You know, as gratifying, frankly, to me to see really what I consider substantial improvements in the collaborative effort to accomplish our mutual goals with the Agency, I can tell you, as I said, having been around this industry for a long time, the flexibility that we see, the interest in regular communication and working together because these really are mutual goals, right, and they are, as always, in the interest and the best interest of the patients. So thank you to the panel, and that's all I have.

MR. SPEER: Okay.

DR. LOYO-BERRIOS: Thank you. We give it back to Jon.

MR. SPEER: Okay, great. Russell and Nilsa, thank you so much and thank you to the panelists, as well as to all of the Session 2 presenters. Great information shared in this, as well.

So now we're going to take a quick break, we're going to come back at 2:15 p.m. Eastern Time, so it should be about five and a half minutes or so. So a short break, but we'll come back and resume with Session 3 at 2:15 p.m. Eastern.

(Off the record at 2:10 p.m.)

(On the record at 2:15 p.m.)

MR. SPEER: All right, that was a quick break, but thank you for your flexibility. We're cramming a lot of information into today's workshop, I hope you're getting a lot of value out of it. So we're about to start our third and final session for today and in this session we're going to cover topics related to inspections and postmarket approval

reporting.

So first let me introduce the first presentation and it is about Medical Device Single Audit Program. The presenter is Lieutenant Commander Jacob Dyer with FDA. Lieutenant Commander Dyer is a senior regulatory officer in the Regulatory Inspections and Audits Team at CDRH's Office of Regulatory Programs. He is currently serving as the program analyst and assessor for the Medical Device Single Audit Program where he leads efforts associated with MDSAP development and implementation with other regulatory authorities and industries. So please proceed.

LCDR DYER: Hello, my name is Lieutenant Commander Jake Dyer. I'll be providing an overview of the Medical Device Single Audit Program and talking about how the FDA utilizes this data in postmarket activities. Thank you for joining us.

During today's session, our learning objectives will be reviewing MDSAP updates, describing how FDA uses MDSAP, and we'll go over the MDSAP transmittal that describes COVID-19 measures and remote auditing.

So it can't be an FDA presentation without acronyms. So the first one is the Medical Device Single Audit Program, often referred to as MDSAP. The next is the regulatory authority or RAs, and these are the organizations like the FDA and Health Canada. And then we have auditing organizations or AOs. These are the third-party organizations that are performing MDSAP audits.

The Medical Device Single Audit Program, or MDSAP, acts as a third-party inspection program. The three major participants are the regulatory authorities, the auditing organizations, and the manufacturers.

The auditing organizations conduct annual audits of participating manufacturers and certify these manufacturers. In turn, the AOs are assessed and recognized by the RAs, enabling them to be able to conduct the audits on behalf of MDSAP. The AOs then share

the audit report documentation and outcomes with the RAs. The RAs receiving this information will then make requests to manufacturers to request additional information and they'll provide that information to the RAs. All of this gathered information is then used for the RAs to make regulatory decisions.

Participation starts with education. There are 10 CDRH Learn MDSAP modules on the web. You can look under postmarket activities, inspections, and global harmonization.

The program is recognized and maintained by the five regulatory authorities. They are Australia's TGA; Brazil's ANVISA; Canada's Health Canada, which is also important to note that MDSAP is a mandatory requirement within Canada; Japan's Ministry of Health, Labor and Welfare and the Japanese Pharmaceuticals and Medical Devices Agency; and the U.S. Food and Drug Administration.

There are three official observers: the European Union, the United Kingdom's MHRA, and the World Health Organization uses the program during prequalification of in vitro diagnostics.

Additionally, there are three affiliate members: Argentina's ANMAT, the Republic of Korea's Ministry of Food and Drug Safety, and the newest affiliate member is Singapore's Health Science Authority. And we're always adding new AOs.

The affiliate membership program began in June 2019. This program allows for regulatory authorities to become members of the MDSAP program. However, the requirements of the affiliates are not included in the audit approach. The affiliate members benefit through a capacity building relationship which includes training, information exchange, and assisting with the development of regulatory frameworks.

There are obligations that the affiliate members need to meet. As part of the commitment to the MDSAP, affiliate members need to provide annul reports to RAs which include a discussion of how the member uses the MDSAP program and the audit reports.

The affiliate members are Argentina's National Administration of Drugs, Foods and Medical Devices or ANMAT, the Republic of Korea's Ministry of Food and Drug Safety, and just recently added is Singapore's Health Sciences Authority.

It's important to note that affiliate members may receive audit reports and certificates only if your facility submits these documents to the affiliate members. Affiliate members do not have access to the regulatory platform maintained by the RAs.

The program has largely remained the same throughout the past year, however, there are some areas to highlight.

Here is a quick snapshot of the number of manufacturing locations that participate in MDSAP. We currently have approximately 5800 manufacturing locations that participate in the program worldwide.

From 2018 to 2020, you can see that there has been steady growth in the program. Due to travel restrictions caused by the pandemic, we have seen a slowdown in growth. We expect these numbers to continue to grow after restrictions throughout the world are lifted and areas begin to open back up.

There are currently 15 AOs that are either authorized or recognized to conduct MDSAP audits. The four AOs on the left have submitted their application to the consortium and RAs have conducted both the Stage 1 and Stage 2 audits. These AOs have met the preliminary requirements to be authorized. The first three MDSAP audits performed by these AOs are witnessed by the RAs.

In the middle are the 11 fully recognized AOs. To be fully recognized, the AO must have had three witness audits and have adequately addressed all nonconformances. Once recognized, they will be subject to head office assessments and annual witness audits. Additionally, there is currently one application pending, which is DNV GL Presafe out of Hovik, Norway.

The complete list of auditing organizations is located on the MDSAP website and the link will be provided at the end of the presentation.

So with all this data coming in, how does the FDA utilize MDSAP in its day-to-day operations? One thing that hasn't changed since day 1, the FDA will still accept MDSAP audit reports for FDA routine inspections. What this means is that MDSAP participating manufacturers are exempt from FDA routine inspections.

However, there are inspection levels and situations listed in the Compliance Program Guidance Manual (CPGM) 7382.845, titled "Inspection of Medical Device Manufacturers." Those still apply.

Here we take a look at the other FDA quality system inspections that are exempt and not exempt if you participate in MDSAP. So for example, in the green box, "routine" fall under inspection levels 1 and 2, these fall into the exempt category. The other levels, 3, Special, Pre- and Postmarket are not exempt. These are either compliance follow-up, for-cause, risk-based work plan, and PMA approval inspections. These levels, 3, Special, and PMA, you are not exempt, so an FDA investigator may call to preannounce an inspection for these types of inspections.

The types of FDA inspections and types of MDSAP audits are shown in this table. As noted previously, MDSAP participants are not exempted from risk-based inspections. Additionally, the MDSAP audit approach utilizes a 3-year cycle. There's an initial, a certification decision, two surveillance audits, and then a recertification followed by a certification decision. So the certification decision is made after the initial and recertification cycles.

MDSAP audits and FDA inspections share many similarities. For example, ISO 13485 plus regulatory authority requirements are used for MDSAP audits. For FDA inspections, they're largely focused on 21 C.F.R. 820, 803, 806, and 807.

MDSAP is a voluntary program in the U.S. However, FDA inspections are mandatory. As noted previously, FDA will accept MDSAP audit reports for FDA routine inspections.

For MDSAP, a third-party auditor is used and these come from the auditing organizations. For FDA inspections, an FDA investigator is utilized.

MDSAP follows the MDSAP audit approach, while FDA inspections follow the quality system inspection technique or QSIT.

MDSAP audits have routine inspection equivalency, so for initial, surveillance, and recertification audits. For FDA inspections there's baseline, abbreviated, EPRC, for-cause, and risk-based work plan. And as we spoke about, just the routine ones the MDSAP audit will cover.

The MDSAP audit report and NGE form are deliverables that come out of the MDSAP audit. They're very similar to the EIR and FDA 483 from an FDA inspection. The audit report is akin to the EIR and the NGE form is very similar in many ways to the FDA 483.

A single MDSAP audit covers multiple regulatory authorities while an FDA inspection really covers the FDA's requirements.

The COVID-19 pandemic has limited travel and impacted the ability to conduct in-person audits. MDSAP Transmittal 2020-10 was released on 12/31/2020. This transmittal supersedes the previous transmittal, 2020-07, and focuses on the extension and expansion of temporary extraordinary measures related to the MDSAP audits during COVID-19 quarantine orders and travel restrictions. This transmittal describes the interim measures to address challenges. It also covers and focuses on remote audits as a substitute for on-site audits.

So alternative audits arrangements can only occur when travel restrictions and social and physical distancing are in place as a result of the pandemic. A risk-based process is used to determine the type of alternative audit allowed. Evaluation of audit history, device

type, and complexity of manufacturing drives the type of alternative audit type used under this MDSAP transmittal. For example, a U.S. Class III device manufacturer would typically undergo a hybrid audit under Transmittal 2020-10. The requirements to audit are still present and AOs are expected to suspend or withdraw certification if they are not able to certify the manufacturer utilizing Transmittal 2020-10. For such situations, regulatory authorities would have to exercise judgment on the device licensing and marketing authorization based on the impact to public health.

So the four types of alternative audit types that are discussed in part of that transmittal is a desktop audit, so it's an audit performed remotely by reviewing documentation; a remote audit, which is an audit performed off site using information and communication technology or ICT. Then there's the hybrid audit, audits partially performed off site with at least one MDSAP qualified auditor that's simultaneously on site during a portion of the audit. And then there's also surrogate audits, where the audit is partially performed off site using ICT while at least one non-MDSAP qualified auditor is simultaneously on site during a portion of the audit. These different situations have had to come up due to travel restrictions and having expertise in the same area as the facilities many times.

Throughout the year, AOs have been performing remote audits of manufacturers. Additionally, RAs have been performing remote witness audits and head office assessments of AOs, though it has not gone without any challenges. Technology, for example, has been a challenge, coordinating the different ICT systems between AOs and manufacturers as well as RAs. There's video and audio quality issues sometimes and the occasional connectivity issue. Being an international program, many times RAs and AOs are in different parts of the country and/or world. Travel restrictions have made it -- have posed problems making it hard to plan both hybrid and surrogate audits. With facilities closed, availability of

resources has caused problems. And the uncertainty of the pandemic has made it difficult to schedule and plan out audits by both the AOs and the RAs.

In summary, MDSAP allows a single regulatory audit that satisfies the requirements of multiple regulatory jurisdictions.

Audits are conducted by third-party auditing organizations. These auditing organizations are assessed and recognized by the RAs.

Results from MDSAP audits are factored into compliance activities.

In June of 2019, the affiliate member program launched and there's currently three affiliate RAs.

And extraordinary measures had to be implemented for remote and off-site auditing due to the COVID-19 pandemic.

This slide contains a list of resources that were cited throughout the presentation.

MR. SPEER: Okay. Thank you, Lieutenant Commander Dyer.

Again, remember, if you have questions and comments throughout the remaining presentations, you can e-mail those at oht6-feedback@fda.hhs.gov.

Let's move to our next presentation and this is about inspections and establishment inspection reporting, and the presenter will be John Gomes from FDA. You'll recall, John was one of our moderators in an earlier group discussion. So John, go ahead, please.

MR. GOMES: Good afternoon, everyone, my name is John Gomes. I'm a lead reviewer in the Office of Orthopedic Devices with a background in electrical engineering and over 9 years of experience with medical device compliance.

Today's presentation is designed to give you a high-level overview of FDA's inspection process, what information is reviewed during an inspection, type of records generated during and after inspections, how FDA reviews inspectional information, and what are the possible regulatory outcomes after an FDA inspection is completed. We will

also present some inspectional data related to device inspections.

FDA inspects manufacturers or processors of FDA-regulated products to verify that they comply with relevant regulations and to ensure that products reaching consumers are safe. FDA's inspection authority is granted under Section 704 of the Food, Drug, and Cosmetic Act. Specifically, Section 704(a)(1) states that FDA officers or employees are authorized to enter any factory, warehouse or establishment in which FDA-regulated products are manufactured, processed, packed or held in order to inspect that factory, warehouse or establishment.

Inspections may also include, and often include, all the relevant equipment, finished and unfinished materials, containers, and labeling. This may also include any vehicle being used to transport or hold such FDA-regulated products.

As you can see, Section 704(a)(1) states that FDA inspections be conducted at reasonable times, within reasonable limits and in a reasonable manner. Although the FD&C Act does not specifically define "reasonable," FDA has long maintained that the inspectional authority extends to what is reasonably necessary to achieve the objective of the inspection. FDA intends to work with facilities to conduct inspections and obtain necessary information to achieve the objectives of an inspection.

Please note that it is a prohibited act under Section 301(e) and 301(f) of the FD&C Act to refuse to permit entry or inspection or refuse to permit access to or copying of certain specific records.

FDA's inspections are not limited to only domestic inspections. Foreign establishments that manufacture, process, pack or hold FDA-regulated products for introduction into the U.S. interstate commerce are also inspected. Just to give you an idea, in fiscal year 2019, before the onset of the COVID-19 pandemic, FDA had conducted a total of about 13,000 domestic and over 3,000 foreign inspections. Of these, there were over

1500 domestic device inspections and almost 400 foreign device inspections.

Next, I will discuss the different types of FDA inspections conducted at medical device manufacturers.

Inspections can be conducted for a device for which a premarket approval application, also known as a PMA, or Humanitarian Device Exemption or also known as an HDE, has been submitted for approval.

When a manufacturing site of a PMA device changes, FDA may also inspect the new site before approval of the site change.

Routine surveillance inspections are conducted for establishments that have not been inspected or some time has elapsed since the last inspection. FDA also recognizes MDSAP audits for firms that are in the MDSAP program, as discussed in a previous presentation.

FDA may also conduct for-cause inspections if specific concerns are identified during internal investigations of allegations or safety signals or if there is a need for a follow-up after regulatory actions such as issuance of a warning letter.

Finally, FDA also conducts risk-based inspections. The risk analysis is conducted through use of data, such as premarket submissions, recalls, and MDR, to identify specific device product codes and to select and prioritize sites for inspections.

What will be covered during an FDA inspection will depend on several factors such as the reason and objective for the inspection, if there was a previous inspection that identified violative conditions, if there is a need for follow-up on past corrective actions, etc.

Typically, an FDA inspection will verify a firm's compliance with the quality system, medical device reporting, corrections and removal, registration and listing, and medical device tracking regulations as shown on this slide.

The scope of the inspection will also depend on the scope of responsibility of the establishment being inspected. For example, if an establishment is not responsible for any part of the MDR process, the MDR portion of the inspection will not be covered during that inspection. However, the establishment that is responsible for MDRs will be identified and noted in the inspection report.

FDA investigators typically also review MDRs, including a firm's MDR procedures, any corrections or removals that may have been conducted and not reported to FDA, and significant design or manufacturing changes that may have been implemented without proper notification to the Agency.

This slide shows a general flow of FDA inspections, which may start with a prior notice of inspection. Please note that depending on the circumstances and the objectives of the inspections, FDA may not provide prior notice of inspection and may conduct an unannounced inspection.

After arrival at the inspection site, investigators will present their credentials and will issue the notice of inspection, or Form FDA 482, to the management of that establishment. It should be noted that a notice of inspection is not required to be issued during foreign inspections.

The process continues with the actual inspection, which may include requests for, and collection of, relevant documents, also formally known as exhibits.

At the close of the inspection, the investigator may conduct a meeting with the firm's management to discuss potential violative situations and other situations that may be concerning. If violative conditions have been formally documented, the investigator will issue the inspectional observations form, also known as Form FDA 483. I will elaborate more on the FDA 483 on a different slide.

Once the inspection has been officially closed, the process continues with

preparation of the establishment inspection report, also known as EIR, followed by a detailed review of the EIR and associated exhibits by FDA staff. Finally, after review of the inspectional evidence and if warranted, appropriate regulatory and administrative follow-up can be taken by the Agency.

As was discussed earlier, several regulations may be covered during an FDA inspection and one of the main regulations is the quality system regulation covered under 21 C.F.R. 820 which governs the methods, facilities, and controls used for the design, manufacture, packaging, labeling, storage, installation, and servicing of finished medical devices.

The approach used by FDA investigators to cover the quality system regulation and other related regulations discussed earlier is referred to as quality system inspection technique or QSIT. In the QSIT approach, the quality system regulation is divided into seven subsystems, as shown on the slide. Four of them are considered major subsystems since they are the basic foundations of a firm's quality system. They consist of management control, corrective and preventive actions or CAPA, design controls, and production and process controls.

The QSIT top-down approach begins each subsystem review with an evaluation of whether the firm has addressed the basic requirements in that subsystem by defining and documenting appropriate procedures. This is followed by an analysis of whether the firm has implemented the requirements of that subsystem.

This slide gives you a high-level overview of the two primary documents that are generated from an FDA inspection. The inspectional observations form, also known as the FDA 483, is issued to a firm only if potential violative conditions are observed during the inspection.

The 483 consists of what are called observations, in other words, the deficiencies

observed by the FDA investigator during an inspection. Each observation includes two components, a high-level description of the deficiency that references requirements of a specific regulation. This is followed by a detailed description of the specific deficiency.

Please note that firms can provide a written response to the observations cited in the FDA 483 within 15 days after the close of the inspection. We highly recommend that firms provide a written response to the FDA 483 since it is taken into consideration during review of the EIR and determination of any regulatory follow-up.

Establishment inspection reports, also known as EIRs, are always generated after an inspection. This is a detailed report of each regulation covered, documents collected, processes and equipment examined, and observations noted by the investigator during the inspection.

Each FDA 483 observation is also discussed in detail with the references to appropriate exhibits collected during the inspection. Finally, any topics discussed with the firm's management at the end of the inspection is also documented.

So what does review of an inspection involve and what does it mean? An inspectional review includes review of the FDA 483 if issued, the EIR, which may include various exhibits collected by the investigator, and any response received from the firm. Exhibits may include standard operating procedures, design, production, shipment, marketing records, and pictures taken during inspections. During the review, the supportability of each observation cited in the FDA 483 is also verified.

Please note that a detailed review of the EIR and exhibits may uncover additional violative conditions not documented in the FDA 483.

After review of all inspectional information, each inspection is classified into one of three categories:

- No action indicated, or NAI, meaning no objectionable conditions or practices

were found during the inspection.

- Voluntary action indicated, or VAI, meaning objectionable conditions were found and documented, but the Agency is not prepared to take or recommend any regulatory actions because the objectionable conditions do not meet the threshold for regulatory action.
- Official action indicated, or OAI, meaning objectionable conditions were found and regulatory action should be recommended.

So what type of regulatory follow-up actions are considered? And how is an action chosen? FDA may consider several regulatory follow-up actions such as an untitled letter, a warning letter, a regulatory meeting, recall, seizure, injunction, or civil money penalties.

FDA uses patient-focused benefit-risk assessments for determining the need and the type of regulatory follow-up actions.

Several factors are considered in FDA's benefit-risk assessments, such as type of device involved, significance of individual violative observations, and the potential for patient harm or the potential for distribution of nonconforming products; combined effect of related observations that can affect the benefit-risk profile of a device; number of serious adverse events involved; firm's response to the FDA 483 and firm's regulatory history. FDA may also consider factors such as magnitude and duration of beneficial effects of the device involved and medical necessity of the device.

This concludes the high-level overview of FDA's inspection process. In the current and the next few slides, I will present historical data related to FDA's device inspections as a reference.

This slide shows the number of domestic and foreign device inspections conducted from fiscal year 2009 until 2021. Please note that the 2021 data was pooled in April and does not represent the complete fiscal year.

As you can see, FDA conducts hundreds of inspections just under its device portfolio every year, both domestically and internationally. It is worth noting that in the year of 2020, FDA did not conduct as many inspections as previous years due to the COVID-19 pandemic. Recently, FDA has started conducting inspections based on the criticality of the inspectional objectives, and also based on various levels of health risks posed by the COVID-19 pandemic at different geographical areas.

This graph shows the number of device inspections classified into NAI, VAI, and OAI categories from fiscal year 2009 until 2021. Of the roughly 40,000 total device inspections conducted between fiscal year 2009 until 2021, 57% were classified as NAI, 37% as VAI, and 6% as OAI. In general, we recommend companies to engage and collaborate with the FDA if objectionable conditions are found during an inspection.

This graph shows the top 10 observations from the device inspections conducted from fiscal year 2009 until 2021. As you can see, observations related to inadequate CAPA, complaint, and MDR procedure constitute over half of the total number of observations.

Before concluding the presentation, I would like to point you to some resources that may facilitate further understanding of the FDA inspectional process. They are all publicly available on line.

The Compliance Program Guidance Manual, or CPGM, the QSIT and the Investigations Operations Manual, or IOM, include additional information about the inspection process. The Regulatory Procedures Manual, or RPM, includes additional information on various regulatory actions FDA may consider after an inspection.

Thank you for joining in this presentation and I hope that it has provided you with a high-level understanding of FDA's inspection process, regulations, inspectional records, the inspection review process, and the method and the value of engaging with the FDA when objectionable conditions are identified during an inspection.

MR. SPEER: Okay. Thank you, John Gomes.

Let's move on to our next session and it will cover premarket approval manufacturing quality system review, and our presenter is Zhijiang He from FDA. Dr. He is a TPLC lead reviewer in Knee Arthroplasty Devices Team in OHT 6 with both premarket and postmarket review experiences.

DR. HE: Good afternoon, my name is Zhijiang He and I am a lead reviewer in the Knee Arthroplasty Devices Team within OHT 6, Office of Orthopedic Devices. Today I will be presenting on the quality system manufacturing module review for premarket approval submissions. Sometimes it also referred as PMA GMP or good manufacturing practices review.

During this presentation, I will start off by giving you a brief introduction about the PMA program and then discuss the actual PMA submission requirements, specifically those related to quality system manufacturing module, and we will focus the discussion on original PMAs and site change supplements.

FDA classifies devices into three classes. Class I is the lowest risk, Class II is moderate risk, and Class III is the highest risk. Class III devices are devices that support or sustain human life, are of substantial importance in preventing or diagnosing illness or disease, or present a potential unreasonable risk for illness or injury. For these types of devices, there is insufficient information to assure the reasonable assurance of safety and effectiveness solely with general and special controls.

The regulatory pathway utilized to market a Class III medical device is the PMA pathway. A PMA is the most stringent marketing application for a medical device in the United States.

The total review time for a PMA is 180 days. In this slide, the top figure represents the premarket review timeline and the bottom one represents the quality system

manufacturing module review timeline. These are parallel reviews that occur at the same time and comprise as part of the final determination or the product under review. I will focus on the second figure in this presentation.

The review team will review the manufacturing section within 30 days and decide if a preapproval inspection is needed. From Day 30 to Day 60, the reviewer will try to perform interactive review with the sponsor to resolve any outstanding quality system manufacturing module deficiencies. We recommend the sponsor provide requested information as soon as possible to avoid delays in the review process.

From Day 60 to Day 90, the preapproval inspection will be conducted by Office of Regulatory Affairs (ORA) if it is needed. After the inspection, the investigator will generate establishment inspection report (EIR) and it will be reviewed by appropriate teams in ORA before CDRH receives it by Day 120. The EIR report will be reviewed from Day 120 to Day 150 by CDRH. Therefore, to ensure smooth PMA quality system manufacturing module review process, it is very important that the manufacturing facilities are ready for the inspection and the sponsor provides complete documents for review.

The quality system manufacturing module for an original PMA submission is reviewed by CDRH. The submission should include information outlined in the FDA guidance document "Quality System Information for Certain Premarket Application Reviews." The requirements in this guidance are consistent with 21 C.F.R. 820, including quality system regulation requirements. They are divided into two sections, the site controls and manufacturing controls.

The quality system manufacturing module should include a cover letter. I would like to point out that along with other information, it is recommended to list on the cover letter the date the facilities responsible for design or manufacturing of finished devices are ready for inspection. We recommend you provide an overview of what the quality system

manufacturing module contains and how it is organized. In addition, a device description and an overview of the manufacturing facilities along with the associated firm establishment identification (FEI) number should also be provided. Your quality manual and a list of the standards used in the manufacturing process are also required.

As previously mentioned, there were two principal component sections for the quality system guidance. The first section describes the site control requirements related to design input, design output, design review, design verification, design validation, design transfer, design changes, and design history file of the subject device.

The second principal is related to manufacturing information and other key required procedures, such as complaint handling and CAPA, to ensure the facility has a good quality system and is capable of manufacturing devices meeting specifications. In addition to help facilitate the review, it is recommended to provide a narrative summary of the procedures and referencing the locations of attached procedures in the submission. Providing separate volumes of quality system manufacturing module for different manufacturing sites or vendors is also highly recommended to ensure it is as clear as possible what each facility is responsible for and how they comply with the quality system requirements.

It is worth noting that in orthopedics, each component of the devices is considered a finished device. For example, each component of the hip or the knee system, as illustrated, is considered a finished device. Therefore, if there were multiple contract manufacturers responsible for manufacturing the subject device system, it is recommended all procedures be provided for each of the facilities.

During the PMA quality system manufacturing module review process, CDRH review team will review the provided quality system manufacturing module according to the guidance document concurrently with the premarket review. If there are deficiencies in the quality system manufacturing module, these deficiencies will be communicated to the

sponsor in a formal deficiency letter or via e-mail through an interactive review process. In addition, CDRH collaborates with ORA to schedule any preapproval inspections, if it is necessary.

Prior to the approval of a PMA application, CDRH will typically issue an inspection assignment for manufacturing sites that are deemed necessary to be inspected. That determination is made based on the history of the responsible sites. In some cases, a postmarket inspection may be recommended in lieu or in addition to preapproval inspections. The inspections will be coordinated with the sponsor and conducted on or up to the date the sponsor indicates in the cover letter that the sites will be ready for inspection. It is important to ensure the sites are ready for inspection prior to submitting a PMA submission to prevent any delays in the approval.

A PMA postmarket inspection is typically conducted 8 to 12 months after the PMA has been approved. This device-specific inspection is intended to assure that the manufacturer is making the device in accordance with the conditions specified in the PMA and that it complies with the requirements of the QS regulation, MDR regulation, corrections and removal regulation, registration and listing regulation, and medical device tracking regulation.

After approval of your PMA submission, you may want to introduce a new manufacturing site for your PMA device or introduce new manufacturing opportunities in a site that was approved for your PMA device already. In these situations, you will need to submit a site change supplement for your PMA. For site changes, all manufacturing requirements, with the exception of design controls previously discussed, are the same. Please follow the suggestions on FDA guidance document "Manufacturing Site Change Supplements: Content and Submissions." This guidance is intended to help industry decide when a change in the manufacturing site should be submitted in a PMA site change

supplement. The guidance is only intended to help industry anticipate when a preapproval inspection in connection with a PMA manufacturing site change supplement will likely be needed to evaluate the firm's implementation of the QS regulation requirements in 21 C.F.R. Part 820. As a result, this guidance should help firms manage the time frames associated with implementing the changes in a manufacturing site and any processes, factors, procedures, qualifications, and validations.

To ensure a smooth PMA quality system manufacturing module review process, please follow the three key strategies: be organized, be prepared, and be responsive. Your quality system manufacturing module should be well organized and complete. The manufacturing sites should be ready for quality system inspections. You should provide responses to FDA's deficiency questions in a timely manner. And if you are not clear about a question from FDA, please contact the review team to ask for clarifications.

MR. SPEER: Okay. Thank you, Zhijiang.

DR. HE: Thank you.

MR. SPEER: Thank you. Let's move to our next presentation and the next presentation is 30-day notice versus annual report. Two presenters. The first is Dr. Ting Song from the FDA. Dr. Song presented earlier today.

And also joining from FDA is Dr. Sita Modali. Sita Modali has been working as a lead reviewer in the Division of Joint Arthroplasty Devices, Knee Arthroplasty Devices Team within the Office of Health Technology 6 at FDA since 2019.

DR. SONG: Good afternoon, my name is Ting Song. Today Dr. Sita Modali and I will present PMA 30-day notice and annual reports. Dr. Modali is a biologist and a lead reviewer in the Knee Arthroplasty Devices Team in the Office of Health Technology 6, Office of Orthopedic Devices. And I am the assistant director of the knee team.

First, we would like to introduce different types of PMA supplements and reports.

Then we will explain 30-day notice and annual report best practices and provide orthopedic device-related examples.

There are six types of PMA supplements including panel track supplement, 180-day supplement, real-time supplement, 30-day notice, special supplement or changes being effected, and site change supplement. If the changes do not affect the safety or effectiveness of the device, the changes can be included in annual reports. Please refer to FDA guidance "Modifications to Devices Subject to PMA - The PMA Supplement Decision-Making Process."

A primary indicator of what type of PMA submission is appropriate is the nature of the data that is needed to demonstrate the safety and effectiveness of the modified device.

Panel track supplement is for a change in indications for use, design and/or performance. Substantial clinical data is generally necessary to support the change.

One-hundred-and-eighty-day supplement is for a significant change including principal of operation, control mechanism, design, performance, labeling, and new testing or acceptance criteria. Preclinical and in some instances, confirmatory clinical data is needed to support the change.

Real-time supplement is for a minor change for which critical data or FDA inspections are not needed, such as changes in design, software, labeling other than contraindications, or sterilization of packaging.

Special PMA supplement is for a change that enhances the safety of the devices and effectiveness is not changed.

Thirty-day notice is for a change in manufacturing that affect the safety and effectiveness.

Manufacturing site change supplement is for a move to a different manufacturing facility or establishment.

There are four steps to decide the regulatory pathway for a modified PMA device. The first step is to identify the modification and a reason for it. Step 2 is to conduct a risk analysis. Step 3 is to define data to assess the impact of the modification on safety and effectiveness. Step 4 is to decide the appropriate regulatory pathway.

Today we will be focusing on explaining 30-day notice and annual reports because they are the most frequently submitted file types.

Thirty-day notice is appropriate for changes to the manufacturing procedure or changes in the method of manufacture which affect the safety and effectiveness of the device, for example, a change in sterility dose auditing; a manual cutting process to an automated one; adding an automated supplier for a device component and the specifications are the same; a change to the machining lubricant.

A 30-day notice is not appropriate when the changes alter the following:

- Manufacturing or sterilization site of a finished device
- Device design or performance specifications
- Designated physical or chemical specifications such as material specifications of the finished device
- Device operating software

For these changes, other supplement types are more appropriate. We will provide examples in this presentation. Please refer to FDA guidance "30-day Notice, 135-day PMA Supplements, and 75-Day HDE Supplements for Manufacturing Method or Process Changes."

The PMA applicant is primarily responsible for determining if changes do not impact the safety or effectiveness of the device, and that's appropriate for any reports. For each change that was identified as annual reportable change that did not require a PMA supplement or a 30-day notice, we recommend you identify the following as applicable:

- Description of the change made, including a comparison to the previously approved version
- Rationale for making the change, including identification of events related to the reason for the change
- Listing or grouping of associated changes that were made to address the same issue
- Scientific or regulatory basis for concluding that the change had no impact on safety or effectiveness in order to allow FDA to understand how the applicant determined the change did not require a PMA supplement or 30-day notice

Please refer to FDA guidance "Annual Reports for Approved PMA."

Next, Dr. Modali will explain best practices and provide orthopedic device-related examples.

DR. MODALI: Thank you, Dr. Song.

So far, Dr. Song has explained what kind of changes are appropriate for a 30-day notice and what kind of changes are appropriate for an annual report. Now let's see what are the best practices for submitting a 30-day notice.

The following items shall be included in a 30-day notice:

- A description of the change
- A summary of the data or information supporting the change (example, a few concise pages summarizing test method, acceptance criteria, samples tested)
- A statement that the change has been made under the requirement of 520(f) of the Food, Drug, and Cosmetic Act and 21 C.F.R. Part 820

Additionally, 30-day notice should also contain the following items:

- A description of the device
- Identification of the manufacturing facilities where the change will be

implemented

- Reason for the change, including a description of any adverse events or field failures that have occurred
- Recall
- Corrective and preventive actions
- Appendices of supporting data where appropriate

The summary of the data or information supporting the change should include:

- A summary of the procedures
- Statistical rationale for the sampling method
- A summary of the completed validation study
- A method to monitor and control any changed manufacturing process, etc.

Let's take a look at the best practices to report annual reports. According to FDA guidance "Annual Reports for Approved Premarket Approval Applications," FDA recommends that the applicant provide separate summary tables for manufacturing changes, design changes, and labeling changes, and that the applicant identify changes that are associated with each other so it is clear which changes are linked. For example, certain changes might be linked to each other because they're intended to improve or correct the same aspect of the device.

Please see below table for recommended format for the changes table description. Change order number, type of change, description of change, reason for the change, related changes, why changes do not impact safety and effectiveness should be included in the table.

We emphasize that the applicant should take a few sentences or paragraph documenting why the change does not affect safety and effectiveness.

In addition, FDA recommends the applicant provide clear information for changes,

for example, the applicant can include schematic diagrams; tables comparing pre- and post-change features in the change description as additional examples.

Let's take a look at some orthopedic examples appropriate for a 30-day notice. In the first example, adding a new polishing machine for polishing a ceramic component of the device, this requires evaluation to ensure all critical parameters such as roughness and dimensions remain within the specifications.

In the second example, adding a new corrosion protection oil during manufacturing of components, this requires assurance of cleaning/biocompatibility to ensure this oil does not adversely impact the biocompatibility of the final finished device.

In the third example, adding a new computer numerical control machine for the manufacture of a component of the device, this requires evaluation to ensure the specifications and surface conditions are unchanged for the component.

In the fourth example, changing process parameters of the nitric acid bioburden reduction process for ultra-high molecular-weight polyethylene component, this change is being made to increase process output. This change required evaluation of process validation or qualification and evaluation of any effects on the color change or surface roughness of the ultra-high molecular-weight polyethylene device due to change in the nitric acid properties.

If the change qualifies for a 30-day notice and you have not submitted adequate information within 30 days of receipt, FDA will inform you via e-mail or letter that a 135-day PMA supplement is needed and you should provide additional information to FDA.

Here are some orthopedic samples where a 30-day notice needs conversion to a 135-day supplement. In the first example, change in the coolant formulation that is used in the manufacturing process is made. However, the provided cleaning validation demonstrated residues on the surface and biocompatibility concerns of the residues could

not be resolved interactively. Hence, additional information is needed to evaluate the biocompatibility of the residues.

In the second example, change in direct compression molding process of ultra-high molecular-weight polyethylene component was made. The change is being made to align with direct compression molding process at a different location of the same manufacturer. As the change in temperature and pressure may affect the microstructure specifications and can have a significant effect on the mechanical properties of the device, additional information is needed. In this case, the file may be converted to a 135-day supplement.

Another example, Example 3, change to packaging equipment. The change is being made to replace existing nonconforming sealing equipment. A justification for the sample size/acceptance criteria is required to review the validation of the changes. Additional information is needed as the concern could not be addressed interactively.

Here are some examples of different PMA supplements that are not 30-day notice changes. The first one is panel track supplement. In this example, the PMA device has been approved for one anatomic location, for example, long bones. The applicant has made a change to add a new anatomic location in the indications for use, for example, spine, and provided new clinical data to support this new indications for use.

Next is 180-day supplement. In this example, the applicant proposed to change the material from one specific type of polyethylene to another type of polyethylene, modified the packaging components and materials and requested approval of shelf-life protocol.

Next is real-time supplement example. The package material and configuration was changed. Hence, new package validation and shelf-life testing needed to be evaluated.

And special PMA supplement example. This change is to final specification. The applicant added an additional specification step in manufacturing process to add additional assurance of purity and reliability of the device.

The next is manufacturing site change supplement. In this example, the applicant proposed to move to a different manufacturing facility or establishment.

Here are some examples for annual reportable changes. The first example, movement of manufacturing equipment in the same facility with no other changes, keeping the process flow the same.

The second example, replacement of broken parts as part of routine maintenance with the same equipment.

And the third example, update labels by adding language, unique device identifier, information and data matrix codes to align with current practice.

Here are a couple of examples that are not annual reportable. The first example, change in the sterilization trays. The current sterilization trays used for sterilization of the PMA device-specific instrument is no longer available. Hence, new sterilization trays will be used. Sterilization validation should be conducted using the new sterilization trays. PMA supplement is needed to demonstrate with supporting data that the new trays can maintain sterility under the worst-case sterilization condition.

The second example, change in the formulation of the coolant used in the manufacturing process. The current coolant has a preservative that may have toxic potential or the current coolant is not available. Hence, the formulation of the coolant is changed. Cleaning validation should be conducted and biocompatibility risk assessment should be provided to evaluate the biocompatibility of the coolant residues on the surface. PMA supplement should be submitted to review the adequacy of the biocompatibility risk assessment.

This concludes our presentation and I hope the information provided is helpful. Thank you very much for your participation.

MR. SPEER: All right. Thank you so much, Dr. Ting and Dr. Modali.

We're going to proceed on to our next presentation. The next presentation is industry perspective on inspections and good manufacturing practice review, and the presenters are Jennifer Harris with Acumed/OsteoMed and Erika Guthrie, also with Acumed/OsteoMed. Both ladies presented earlier today, so let's go ahead with the next presentation.

MS. HARRIS: Good afternoon, my name is Jenny Harris and I'm the director of quality for Acumed/OsteoMed based in Addison, Texas. My colleague, Erika Guthrie, who's also the director of quality for Acumed based in Hillsboro, Oregon, and I will be discussing with you today our experiences with inspections, both FDA and other external audits, that we've both experienced.

Here's a few of the topics that we'll be covering. Erika will be reviewing the procedure we have in place for conducting these types of inspections. She'll also share with you the inspection challenges that we've experienced during these visits. I'll be reviewing with you the changes in industry that we've observed over the last few years. I'll also be discussing with you the inspection findings that we've seen. And finally, we'll be both discussing with you many of the lessons we've learned from COVID.

MS. GUTHRIE: Hello. So I wanted to start out by talking a little bit about the inspection procedures that we have in place. You'll see a lot here on these next few slides due to the fact that throughout industry we all have long procedures saying how to do this and it's been incredibly established. However, at the same time, that could show that there could be some places for innovation here, given the amount of innovation done in the rest of industry.

So we all have an initial greeting that we do with auditors and inspectors. It's generally done, at the first, at the front desk where we come to visit them. We make sure they have badges and are set up and ready to go and somebody's with them at all times.

Then we have daily opening meetings where we hold -- you know, the first day will be members of the executive team, there may be smaller groups at each daily meeting after that. We have interview techniques that we go over with individual staff members that we go over quite a bit of the time. We make sure that there's QA personnel with them at all times, and we make sure that if there's any type of misunderstanding or misalignment, that it's closed each day prior to the end of any meetings so that we make sure that we don't leave anything unanswered.

We all have back room support, so we make sure that there's people in the back room who are understanding what's going on in the front room with the auditors and inspectors, and it's the job of this group to make sure that they're getting all of the SOPs, the work instructions, the forms, test reports, whatever is being requested to review is brought up to the front by that team.

We also have daily and final closing meetings much like the opening meetings. The daily close meetings will be a smaller group of people and then the final close meetings for us, at least, will be our executive team. From there, though, we do keep moving for some more information where we have responses to audit findings drafted and submitted within the specified timelines that we discuss during the final closing meetings.

When it comes to challenges that we've had with inspections, there's a few different ones, the first being that sometimes the inspectors that we get have different specialty fields, so we do spend a lot of time bringing products out, explaining how the products work and trying to get through some of the engineering speak that happens on a day-to-day basis within industry to make sure that that's understood by the inspectors as they're reading through documentation. There can be some inconsistency between inspectors where there's different, you know, places of interest that they have, so it may be one inspection we have is all about design control while another one is all about CAPA, for instance. The

methodology varies. Some inspectors truly do follow the QSIT method and some don't. And then there's also no specific cadence to those inspections. So you know, sometimes you'll go through a few years where it's every other year, then you can have up to 5 years in between, as well, where you're not sure when the inspectors are going to come in.

MS. HARRIS: Some of the things we wanted to discuss today are changes that we've seen in the industry over the last few years and I know many companies are experiencing this, as well. What we're noticing is having a notified body with our international presence in our companies, we get to gain that experience with these constant contacts. We have a scheme manager that we continually speak with and there's a consistency that we're seeing with the inspection cadences, as Erika mentioned in the previous slide.

There's an annual surveillance, there's an annual unannounced, there's constant tech file reviews, and then microbiology audits for those of us dealing with sterile product. This gets a constant cadence to that that we weren't seeing so much in the FDA inspections. There's also an availability for questions that we're much more comfortable with because we're interacting with these groups more frequently.

And then we wanted to discuss a little bit the fact that information provided to understand the "why" and so that back-and-forth gives us the insight into that a little more than what we're experiencing with the evidence sections. And then finally, the 13485 transition approach, with it not being audits, it's the only way to evaluate a compliance.

When it comes to findings, what we were seeing and what we've experienced with some of our FDA inspections were that things seemed to be very focused on procedural misses but not so much risk based, and what we're experiencing now, more with our notified bodies in those types of inspections, is that's really the point that we're driving to try to keep, make and ensure that those risk-based issues have been addressed and that that's what we're focusing on. It's also been very -- it's very beneficial to understand the

current inspection trends related to our industry, as provided by FDA, we're not seeing a lot of that, so that's something I think we would really benefit from in understanding that interaction and that feedback that we could get from FDA.

And finally, with the MDSAP certification, those findings and trends, we're seeing a challenge with how that scoring takes place and that's been something that we've -- we're getting more used to, but I think that's been something that hasn't been consistent as we've moved forward, and I don't know if Erika wants to add anything to that.

MS. GUTHRIE: Yeah, there's been a little bit of inconsistencies in how the program has laid itself out. You know, we aren't really sure who it is that's reviewing these items. In addition to that, some of the areas that are using that program are still coming out and doing inspections with us. So there's been a little bit of a misunderstanding there of how that's going to play out in the future.

MS. HARRIS: And finally, I think the wild card for all of us in the last year, year and a half, has been how COVID has impacted our businesses, inspections, just life in general, and we have a few lessons learned from COVID.

We've certainly become more nimble. Well, we found out we are more nimble, but not as tech savvy as we thought and by that, I mean we were able to really manage doing remote audits, however, we weren't quite as ready for it as I think we thought we would be. We learned the hard way a few ways. Understanding platform capability, as far as before the audit is scheduled and during the audit, understanding how you're going to conduct those remote audits was super important in making sure that both sides could handle the platform that was selected.

I think one of the biggest challenges we experienced doing remote inspections -- because our inspections with our notified bodies did not stop during this last year -- was conducting manufacturing tours. For our facilities specifically, there's a lot of loud

manufacturing equipment and it's incredibly difficult to make a tour work well. I don't think the audio was difficult for those listening in to the tour, but for those of us conducting the tour, it was very difficult to communicate. So those are some challenges we certainly had to try and overcome.

MS. GUTHRIE: And to add to that a little bit, in some of the preparation and how tech savvy we believed ourselves to be, we really did have to find a way to review and exchange procedures and different data as we were going through these types of audits. You know, we had to find file sharing, we had to find something that was accessible by both parties while we were going through all of these. There were some size limitation issues that we had to overcome and oftentimes it ended up that there were a few things where we used a file-sharing service, but another where we would e-mail things over, it had to all go through one person rather than a few people handing things out.

In addition to that, it completely got rid of the need for a back room. It made it so that we could talk to people and be reviewing these files as we were talking to them about it. It made it much less of a barrier to the rest of the organization. You know, without that physical location but still having that function, it meant that there was a smaller number of people doing that kind of back room setup. It meant that we didn't have to take a portion of the building and say that it was only for this function now.

So it was a lot easier on the organization and that's why we have this last bullet in it about that impact. It was far less impactful for the organization. For instance, when we did a tour, as Jenny was speaking, it may have been a little bit difficult for us to hear, but at the same time it was less people being involved in walking through and listening in and it made it so that more work was done during those times of audit and inspection than had been done in the past.

And then lastly, it really did impact how we did our own internal audits. We've

figured out how to do that file sharing with each other and really worked out the kinks during those processes and those procedures that we were following and we did have to learn some new things along the way but overall, for us, it ended up being the same amount of information as we had in audits before, if not a little bit more, because things moved a little quicker with less impact to the organization, which was really helpful. And I don't know if Jenny has anything she wants to add to that piece of it.

MS. HARRIS: Yeah, I think those are all great points. I think we were surprised by once we got our minds wrapped around it, it went really well.

And that ends our presentation for today. We look forward to any questions and discussion points we'll have during the discussion session. Thank you so much.

MR. SPEER: All right. Thank you, Jenny and Erika, great insights.

So in the interest of time, because we want to end on time today, we're going to go ahead and transition to the group discussion. So let me do a brief introduction of the moderators and panelists.

So joining me as a moderator for this session is Shumaya Ali. Shumaya is with FDA and she serves as the assistant director with the Division of Restorative, Repair and Trauma Devices within the Office of Orthopedic Devices. She oversees the Stereotaxic Bone Growth Stimulators and Fracture Fixation Devices Team, and manages review of both premarket and postmarket programs for these device areas. And Shumaya has been with FDA for 11 years.

So on the panel will be Dhamesh Patel, also with FDA. He has been with the Office of Regulatory Programs since 2019 and he currently manages the PMA, HDE, Q-sub and Device Life Cycle Tracking Team with the Division of Submission Support.

Also from the FDA on the panel is Jhumur Banik. Jhumur is a policy analyst with PMA, HDE, Q-sub and Device Tracking Life Cycle Team in the Division of Submission

Support, Office of Regulatory Programs in FDA/CDRH. She focuses on providing her regulatory and technical expertise for issues pertaining to PMAs, PMA GMP, and Q-submissions for both internal and external stakeholders.

Also joining from FDA is Eric Horowitz. Eric has been with the FDA Center for Devices and Radiological Health since 2003. He is currently a quality system and compliance expert overseeing work with the Center that relates to medical device quality systems, as well as other areas of regulatory compliance and developing compliance policy and processes.

Also joining the panel are earlier presenters, Lieutenant Commander Jacob Dyer from FDA, Stephanie Matthews from Johnson & Johnson, Jenny Harris from Acumed/OsteoMed, and Erika Guthrie from Acumed/OsteoMed.

So Shumaya, do you want to kick the panel discussion off?

MS. ALI: Absolutely. Thank you, Jon, for the warm introduction, and thank you to our panel members in advance for your participation.

So in the next 20 minutes or so, Jon and I will be covering three main areas, FDA inspection, quality system reviews, and post-inspection correspondence, and some of those hot topics everyone may be interested in knowing is the harmonization of FDA quality system regulation and ISO 13485.

So starting with FDA inspection, we have seen FDA presented data on inspection observations and there appears to be ongoing trends with certain quality system deficiencies with CAPA, corrective and preventive actions, process validations and production and process control making it at the top of the list, top 10 inspectional observation list.

So my first question to the panel members is what are some of the best practices manufacturers have adopted or can adopt to help minimize recurrent quality issues?

MS. MATTHEWS: This is Stephanie Matthews, I'm happy to start. Good afternoon,

all. So from a manufacturer's standpoint, several elements. I think certainly having a robust corrective action and preventative action program that consists of also overall monitoring of overall trends in both site and over across franchises. So I think depending on the size of your business, it may look a little differently.

So certainly a best practice is also not just looking at it from a single event perspective, but looking across common equipment, even if a particular product may not have been involved, but certainly looking across your manufacturing sites for either common equipment, common trends. You heard it, that process failure seems to be kind of on top, or inadequacy in the CAPA program to identify other areas of recurrence. So certainly those conversations across even large and small businesses can be really helpful to understand whether the issue can occur in other areas to prevent a future issue.

MR. SPEER: I mean, it's curious to me, I've been studying the annual data year after year and CAPA is always the number one reason why companies get 483 observations and usually, you know, in the top three for warning letters. I'm curious, I guess from both FDA and industry side, why do you think that is?

MR. HOROWITZ: So I'll start that. One common reason that I would say for it is really that CAPA is the heart of the quality system. So when there are problems with CAPA, we at the FDA are going to really hone in on that and pay a lot of attention because it's harder to fix those problems that are in the other areas if your CAPA system isn't working properly. So, part of the reason why that comes up so often is because it is a big focus in our inspections.

But I think part of it also is that I've seen companies struggle particularly with the effectiveness part of CAPA and really being able to take meaningful action and then be sure that the action they're going to take is actually going to fix the problems and prevent recurrence of those issues which then, if you don't have a good system in place for making

sure that that's done well and for having the investigations up front to make sure that you're identifying meaningful actions, then you can end up in a place where you're taking CAPAs over and over again because the actions you took aren't actually fixing the problem or problems.

MR. SPEER: All right, thank you. Any other comments on that before we move to the next question?

MS. HARRIS: This is Jenny with Acumed. I was just going to say I think there's such a fine line and balance between identifying what needs to go into the CAPA system and what doesn't and it's very easy in different places I've been for your CAPA system to get overwhelmed with all the best intentions.

And then, as Stephanie mentioned, those systems identifying what needs to be considered for CAPA are extremely crucial in helping the organization make good decisions about these efforts because, as most of us have developed these systems, CAPA becomes a very big project, typically, and it takes a lot of resources in that continued effort and I think that I know in different places I've worked, that becomes sometimes a struggle to make sure we've got the focus in the right areas, that we can keep that focus continued and don't overwhelm our own systems with some of those efforts.

MS. MATTHEWS: Great points, Jenny. Scope. Scope is critical. And I think Eric also mentioned the recurrence piece and effectiveness monitoring and I think those are excellent points and I think don't hesitate, there can be more than one monitoring measure. I think we're seeing an emerging trend to look at a couple pieces of that, to look at not just the procedure or changes or complaint reduction, but there can be multiple monitoring effectiveness checks that looks at aspects of it. I think that does help ensure that you can progress and you're not getting aging CAPAs, which can be another issue from overwhelming the system.

MS. ALI: Yeah, just a quick follow-up. You know, I think everybody basically touched on the 360 feedback and monitoring for CAPA and we commonly hear that companies are integrating complaint data and MDRs and we all know that there are downsides to both data. So what other field data are considered as part of those monitoring and evaluations to ensure the quality of medical devices?

MS. MATTHEWS: Another few examples, nonconformance, certainly internal, right, near-miss type of activity can be an input to audit feedback. So again, what we can be seeing if we're seeing an overall trend in, let's say, minor nonconformances in similar areas, can certainly look at an opportunity to put in a reduction program.

And then let's not forget preventative. I think that I also want to stress, you know, those might not be always glamorous, but looking at things from a preventative perspective and having opportunities to put that in, in a very well-scoped project and just focused on prevention can be a very effective way, to show that improvement over -- if it's processed and it's product improvement, there's a few other areas also that can be considered.

MR. SPEER: Okay. So let's talk a little about the preapproval inspection side of things. So obviously preparing for an FDA inspection, it can be very resource intensive and I'm curious, from the FDA participants on the panel, what are some of the factors considered to determine a need for an inspection? I mean, what resource can you point to that provides the transparency into this decision and perhaps allows the manufacturer to prioritize resources for the sites that are likely to be inspected?

MS. BANIK: Hi. So there are various factors that FDA considers. When there's a GMP reviewer or a premarket reviewer looking at the information provided, they all may look at the GMP information, but it factors on whether it's a breakthrough device or not, whether there was a prior inspectional history and what's the outcome of that prior inspectional history, so definitely if it's an OAI, it definitely qualifies for requiring an

inspection. However, if it's an NIA or VAI prior inspectional outcome, then there's a benefit-risk approach that's considered. So considering the products that are covered during a previous inspection is -- was there any recall history within the past 3 years or any history of allegations, were there any 483 observations, any repeat observations noted, and also from -- if you may have heard, there's been the case for quality initiative, specifically the voluntary improvement program, and if it's on that list because it's been -- because the firm has been in good compliance, then they can be waived from an inspection. And also if there's favorable MDSAP or ISO 13485 audit outcomes, that can be used to supplement the decision of whether an inspection is needed but just to clarify, it may not be used in lieu of inspection at this time.

MR. SPEER: Obviously, COVID has had an impact on how FDA is able to conduct preapproval inspections. Can you maybe talk a little bit about how the Agency has had to adjust and prioritize those preapproval inspections over the past year and a half or so?

MS. BANIK: So we've been mainly looking at how much of it would -- the product or the device would be serving an unmet clinical need, for instance, and if there are any other devices like that that exist in the market, that definitely influences also as to whether an inspection is necessary and prioritizing it accordingly in terms of need and of course, based on the location, where it is, it impacts whether or not an inspector can actually go out there physically, but those things have been also considered, as well.

MS. ALI: Let's swing to get MDSAP inspection. In today's presentation we heard from both Jennifer and Erika that there has been challenges with MDSAP scoring. So since we have Lieutenant Commander Dyer is also part of our panel members, can you elaborate on what are those challenges and maybe have Dr. -- Lieutenant Commander Dyer respond to that? Erika, respond to that.

MS. GUTHRIE: Yeah, definitely. You know, I can definitely say that within the initial

training that we did for MDSAP, the section on how to figure out the scoring was about a day of a 4-day training with a lot of people really confused about it. Now it's having conversations with those auditors about whether or not what they're looking at is indeed direct product contact or indirect product contact. It's gotten easier over time.

You know, we got into the MDSAP program early enough that it was a learning curve on both sides. The people who were coming in and doing those audits, it was the first time they were doing them, as well, so there were a few phone calls they were making to make sure they were doing the scoring right, too. It's definitely gotten better, but there's those pieces of it where it just leads to different types of conversation where it's what are we actually referring to as the root cause, again, direct or indirect contact of product.

LCDR DYER: Yeah, that's a very important point and we start to see it, it's a continual improvement process, it has grown quite a bit from the inception and through continuing assessing of the system and assessing with the auditing organizations that each of the regulatory authorities play a part in, help to kind of guide that process as we go forward. So it is built, we've seen the same process through some of the similar discussions that you're experiencing, as well.

MR. SPEER: What do you see -- and I guess, first, from that FDA perspective and then second, from an industry perspective, but from an FDA perspective, what do you see are the major challenges of inspections?

LCDR DYER: So I can start, at least from the MDSAP perspective. So this last year has presented a lot more challenges than in past years, just with -- and it was largely -- I thought it was covered pretty good of what the challenges were with remote audits. Walk-throughs are very difficult to perform with laptops and cameras, so it's a little bit different than your traditional where -- my background, I'm an investigator as well for the FDA. So being able to walk the site, you glean a lot more information than what you can see through a camera.

The camera is constantly turned where it wants to be directed and it's oftentimes very beneficial to see the whole picture. So we've found both the technology aspects, each of the RAs and auditing organizations, and then manufacturing sites have different, I guess, software packages and so trying to get everybody on the same sheet of music is sometimes a little bit difficult, it's a little bit more than what you would think.

MR. HOROWITZ: So to speak to it a little bit on the routine inspection when we're not under a COVID kind of perspective, two things that I would want to really see improve in the future is that we sometimes see observations that are built around a company either not having all of the documentation readily available, so we're not able to really get the right people in the room to be able to say hey, this is what was going on because there isn't really a problem, but the company just can't tell us what the actual situation was, so we aren't able to actually be able to have confidence in the company's ability to perform those specific functions.

But also sometimes there's a little bit of a language issue and I don't mean people speaking different languages literally, but more where maybe the nomenclature that's used in ISO 13485 or in other -- or in the pharmaceutical industry, is being used by the company and because of that, it's hard to equate it with the quality system regulation when it comes to an FDA inspection. And I think the more that a company can do to really understand how the words that they use in their own documents equate to what the regulation requires, the easier it is for them to be able to -- when an investigator is there asking them questions about where to find certain things, it's easy for you to say oh, I know what design outputs that are essential for the proper functioning of the device are. We don't call it that, we call it say critical to quality, they're right over here and I can get those for you. And I'm only focusing on that, those aspects, because there are places where it would be very easy for us to have a better inspectional outcome if the right pieces were in place for the inspection to

go more smoothly.

MR. SPEER: Those are great points. I'm curious, from the industry perspective, the same question. What are your major challenges in dealing with inspections? Anything we haven't covered so far?

MS. MATTHEWS: They were very common challenges, I think, with the technology. You know, we definitely had a lot of review sessions after each day with external auditors, whether it be FDA, notified bodies, many examples. Certainly, at the end of each day, what is working, what is not. You know, we've worked through some best practices in terms of file location, your Mbox, and a few other things. I think the setting up of the back room is very different.

So I think understanding your work streams, though, I know continuous kind of feedback in terms of what's working. Google Glass has been used in terms of walking shop floors. We're now starting to finally see a few folks being able to come in a few sites. We've seen it from a direct inspection at times. So we are seeing that infrequently. But there are limitations, right, in terms of how many people are on site, distance and other protocols and such.

So I think that the clear communication as to what is anticipated and then I know, internally, we're sharing a lot of best practices and what's working in terms of remote and getting feedback from the audit team in terms of what's working so that we can effectively go through the right amount of documentation effectively because these agendas are very long and to be able to go through that audit prep is a key component. So I think it's very similar to what the Agency is already seeing.

MR. SPEER: Great insights from you all and thank you all so much for your contributions throughout the day.

Shumaya, do you want to summarize Session 3, some of the key points that you

picked up today?

MS. ALI: So in the interest of time, I just want to thank the panelists for your interactive discussion, as well. Like, you know, we have heard some of the areas FDA can take back and revisit in terms of improvement. So we did want to end with FDA advocates for taking quality beyond compliance.

And I want to highlight one paper that was published in 2011, so just to say that we understand there is challenges to quality, and FDA is very much looking forward to working with the medical device communities, including industry as well as our patient population, to understand what those challenges are and to work together to develop some of the strategies to address some of those perceived barriers to device quality.

With that, I'll turn it back over. Back to you, Jon.

MR. SPEER: All right, thank you so much.

Well, folks, we're right there at the end of today's workshop and I want to thank you for participating but don't go yet, we have some closing remarks from William Jung with FDA. Dr. Jung is the director of joint arthroplasty devices division in the Office of Health Technology 6, OHT 6: Orthopedic Devices at CDRH/FDA. Dr. Jung received his bachelor's in chemical engineering and master's and Ph.D. in biomedical engineering from the University of Virginia. Since joining FDA in 2009, Dr. Jung has developed expertise in various areas of device regulations as a reviewer and supervisor. He led the Division of Radiological Health in 2012 to implement total product life cycle (TPLC) transformation. So let me hand it over to Dr. Jung for some closing remarks.

DR. JUNG: Thank you for that introduction. And good afternoon, everyone. It's been a pleasure being with all of you virtually today, and let me begin by acknowledging the tireless and hard work from the staff and organizers who made this workshop possible and run smoothly. And I would like to also thank Mr. Jon Speer for emceeing today's event and

he kept us engaged and on schedule. And special thanks to all presenters for putting together a comprehensive overview of FDA's postmarket regulations, best practices analysis, and case studies.

In addition, the review staff and the leadership in the Office of Health Technology 6, Office of Clinical Evaluation and Analysis, and Office of Regulatory Programs have provided invaluable input to our presentations with respect to an understanding of FDA's postmarket activities related specifically to orthopedic devices.

And I'd finally like to thank all the participants, all stakeholders, from patients and manufacturers, for their perspectives as it is vital for FDA to understand your needs and concerns.

Today we shared with you topics related to recalls, medical device reporting, post-approval and postmarket surveillance studies, inspections, and postmarket approval reporting. An objective of this public workshop was to improve public understanding of medical device postmarket programs and regulatory requirements related to orthopedic devices.

During the morning session, along with the overview of postmarket program requirements and regulations, we have presented our best practices on postmarket reporting to FDA and trends analysis based on what FDA has learned from our experiences in recall and MDR reviews. FDA recognizes that there are challenges that the industry and care providers face in retaining relevant information such as device return or retrieval, off-label use, product end of life, accurate description of events, and health hazard evaluation, etc. We hope that you have found FDA's perspective on best practices and trends of commonly occurring recalls and MDRs to be helpful in improving your reporting requirements, and FDA is always open to support effective communications with patients, care providers, and industry.

In the early afternoon session we have presented a refresher on post-approval studies and postmarket surveillance studies highlighting the regulations and requirements. Based on the FDA's experience in post-approval studies and postmarket surveillance studies, FDA encourages timely communication when facing challenges that would delay or cause inadequate progress of the study. In addition, FDA also encourages sponsors to communicate any potential changes in a study population or study design. This will help us guide through overcoming potential complications when utilizing real-world evidence. Whether the source data is from the U.S. or outside of the U.S., FDA strongly encourages sponsors to communicate on reliability and relevance of leveraging said real-world evidence. FDA does see real benefit and least burdensome pathway in leveraging real-world evidence, so we highly encourage the use of it.

In the late afternoon session, FDA presented overviews on Medical Device Single Audit Program (MDSAP), FDA's inspection and establishment inspection reports, and PMA reporting requirements. MDSAP will reduce burdens on regulators as well as the manufacturers by allowing single regulatory audits that satisfy the requirements of multiple regulatory jurisdictions. FDA, as well as other regulatory agencies as well as industry, has faced many extreme technological challenges in completing audits and inspection protocol due to restrictions, and all stakeholders have faced a similar challenge in having effective communications remotely and we have felt that, obviously, very strongly.

And in closing, we hope that the members of the public gain a best understanding of FDA's postmarket program as well as FDA's perspective from stakeholders. FDA believes that today's workshop will serve as a platform providing an efficient postmarket program that will benefit public health. And FDA thanks you for your participation today and this will conclude our workshop.

MR. SPEER: Folks, thank you so much. I know it's been a long day, there's been a lot

of information, but thank you so much for participating and observing and listening throughout this workshop. And I want to thank FDA personally, it's been a great honor to be the master of ceremonies for today's program, so thank you so much. This concludes the program.

(Whereupon, at 4:00 p.m., the meeting was adjourned.)

C E R T I F I C A T E

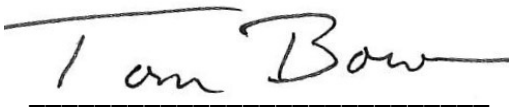
This is to certify that the attached proceedings in the matter of:

VIRTUAL PUBLIC WORKSHOP - ORTHOPEDIC DEVICE POSTMARKET REVIEW

June 10, 2021

Via Videoconference

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.



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