UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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MEDICAL DEVICES ADVISORY COMMITTEE

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GENERAL AND PLASTIC SURGERY DEVICES PANEL

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October 26, 2022

9:00 a.m. EST

Attendees:

Chairperson

Hobart W. Harris, M.D., M.P.H.
Professor of Surgery
Division of General Surgery, UCSF — San Francisco, CA

Non-Voting Members

Karla V. Ballman, Ph.D.
Division Chief of Biostatistics & Epidemiology
Cornell Medicine — New York, NY

Mary H. McGrath, M.D., M.P.H.
Professor of Surgery
Division of Plastic Surgery, UCSF — San Francisco, CA

Susan Galandiuk, M.D..
Professor of Surgery
Division of Colorectal Surgery, University of Louisville — Louisville, KY

Michael DeLong, M.D.
Assistant Professor-in-Residence, Division of Plastic Surgery, UCLA — Los Angeles, CA

Alan Matarasso, M.D., FA.C.S.
Past President American Society of Plastic Surgeons
Clinical Professor of Surgery, Hofstra-Northwell Health System — New York, NY

Andrea Pusic, M.D., M.H.S., F.A.C.S., F.R.S.C.
Chief, Division of Plastic and Reconstructive Surgery, Brigham and Women's Hospital
Professor of Surgery, Harvard Medical School — Boston, MA

Colleen M. McCarthy, M.D.
Plastic and Reconstructive Surgeon, Memorial Sloan Kettering Cancer Center — New York, NY

Kelly Hunt, M.D.
Professor and Chair, Dept. of Breast Surgical Oncology, University of Texas MD Anderson Cancer Center — Houston, TX

Stephen Li, Ph.D.
Biomedical Scientist, Li Consulting — Palm Harbor, FL

Mark D. Soucek, Ph.D.
Professor, Interim Director, School of Polymer Science and Polymer Engineering, University of Akron — Akron, OH

Robert F. Diegelmann, Ph.D.
Distinguished Career and Emeritus Professor, Virginia Commonwealth University School of Medicine — Richmond, VA

Matthew Bloom, M.D., M.S., F.A.C.S.
Trauma and Emergency General Surgery, Critical Care, Cedars-Sinai Medical Center — Los Angeles, CA

Sandra Agazie, R.N., BSN, CMSRN
Chief Executive Officer, Sanzie Healthcare Services, Inc. — Fayetteville, GA

Temporary Non-Voting Members

Deborah Armstrong, M.D.
Professor of Oncology
Department of Oncology, Johns Hopkins University School of Medicine — Baltimore, MD

Andrew Seidman, M.D.
Medical Oncologist, Breast Medicine Service Memorial Sloan Kettering Cancer Center
Professor of Medicine, Weill Cornell Medical College — New York, NY

Melissa Fisher
President, MJF Advisory Services — Marblehead, MA

Industry Representative

P. LaMont Bryant, Ph.D.
Vice President of Regulatory Affairs
Ethicon, Inc.; Johnson & Johnson

Consumer Representative

Rachel S. Brummert
Founder, Quinolone Vigilance Foundation

Patient Representative

Melissa Fisher
President, MJF Advisory Services — Marblehead, MA

Food and Drug Administration

Heather Dean, Ph.D.
U.S. Food & Drug Administration, CDRH — Silver Spring, MD

Binita Ashar, M.D.
U.S. Food & Drug Administration, CDRH — Silver Spring, MD

David Krause, Ph.D.
CDRH/OPEQ/OHT4, Deputy Office Director

Designated Federal Officer

Candace Nalls,

Food and Drug Administration Presenters

Frances Wilder, Ph.D.
Regulatory Advisor, Regulation, Policy, and Guidance (RPG)

Tajanay Ki, B.S.
Biomedical Engineer – Lead Reviewer, CDRH/OPEQ/OHTIV/DHTIVB

Tek Lamichhane, Ph.D.
Senior Staff Fellow – Lead Reviewer, CDRH/OPEQ/OHTIV/DHTIVB

Min Zhang, Ph.D.
General Engineer – Lead Reviewer, CDRH/OPEQ/OHTIV/DHTIVB

Sambasiva Arepalli, Ph.D.
Chemist – Lead Reviewer, CDRH/OPEQ/OHTIV/DHTIVB

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CALL TO ORDER

Dr. Harris: I would like to call this meeting of the General and Plastic Surgery Devices Panel to order. I'm Dr. Hobart Harris, the chairperson of the panel and I'm a general surgeon at the University of California at San Francisco.

I note for the record that the members present constitute a quorum as required by 21 CFR part 14. I would also like to add that the panel members participating in today's meeting have received training in FDA device law and regulations.

For today's agenda, the panel will discuss and make recommendations on the classification proposals for tissue expanders and accessories, mammary sizers, wound dressings with animal derived materials, absorbable synthetic wound dressings, and hemostatic wound dressings with and without thrombin, nail prosthesis, ultrasonic surgical instruments, single use reprocessed ultrasonic surgical instruments, and neurosurgical ultrasonic instruments.

Before we begin, I would like to remind the public and panelists that this is a nonvoting meeting and ask our distinguished committee members and FDA attending to virtually introduce themselves. Committee members, please turn on your video monitors if you have not already done so and unmute your microphone before you speak. I will call your name. Please state your area of expertise, your position, and affiliation. And I apologize beforehand if I butcher anyone's last name. First, Dr. Karla Ballman.

Dr. Ballman: Hi. I'm Karla Ballman, and I am at Weill Cornell Medicine in New York. I'm a Professor and Division Chief at Biostatistics. My area of expertise is biostatistics.

Dr. Harris: Thank you. Dr. Mary McGrath.

Dr. McGrath: Good morning. My name is Mary McGrath, and I'm a plastic surgeon. My position is a Professor Emeritus at the University of California San Francisco and my areas of expertise have to do primarily with breast surgery and wound healing.

Dr. Harris: Thank you. Dr. Susan Galandiuk.

Dr. Galandiuk: I'm a professor of surgery and a colorectal surgeon at the University of Louisville.

Dr. Harris: Thank you. Dr. Michael DeLong.

Michael DeLong: I'm Mike DeLong. I'm an assistant professor in residency at UCLA in plastic surgery and microsurgery. My research interests are in medical devices and regulatory science.

Dr. Harris: Thank you. Dr. Andrea Pusic.

Dr. Pusic: Good morning. I'm Andrea Pusic. I'm a plastic surgeon. I am Chief of Plastic Surgery at Brigham Women's Hospital, Professor of Surgery at Harvard Medical School, Director of the Patient Report Outcomes Healthcare Values Center at the Brigham Women's, and co-chair of the US National Breast Implant Registry.

Dr. Harris: Thank you. Dr. Colleen McCarthy.

Dr. McCarthy: Good morning. I'm Colleen McCarthy. I'm a plastic surgeon. I'm an attending surgeon at Memorial Sloan Kettering Cancer Center and co-chair of the US National Breast Implant Registry and PI of the PROFILE Registry.

Dr. Harris: Thank you. Dr. Andrew Seidman.

Dr. Seidman: Good morning. I'm Dr. Andrew Seidman. I'm a Breast Medical Oncologist here at Memorial Sloan Kettering Cancer Center, where I am an attending physician, and I am a Professor of Medicine at the Weill Cornell Medical College.

Dr. Harris: Thank you. Dr. Deborah Armstrong.

Dr. Armstrong: Hi. I'm Deb Armstrong. I'm a Medical Oncologist at Johns Hopkins in Baltimore, Maryland. I'm a Professor of Oncology. I'm also a former member and Chair of the Oncology Drugs Advisory Committee to FDA.

Dr. Harris: Thank you. Dr. Kelly Hunt.

Dr. Hunt: Hello. I'm Kelly Hunt, and I'm a professor of Surgical Oncology at the MD Anderson Cancer Center, and I am also Chair of the Department of Breast Surgical Oncology at MD Anderson.

Dr. Harris: Thank you. Dr. Mark Soucek.

Dr. Soucek: It's Soucek. Thank you. I am interim director of the School of Polymer Science and Polymer Engineering. I am a polymer materials expert.

Dr. Harris: Thank you. Dr. Robert Diegelmann.

Dr. Diegelmann: Hi. My name is Bob Diegelmann. I'm the Professor Emeritus at Virginia Commonwealth University School of Medicine and my area of expertise is tissue injury and repair.

Dr. Harris: Thank you. Dr. Matthew Bloom.

Dr. Bloom: Good morning.

I'm an associate Professor of Surgery at Cedar Sinai Medical Center, where I practice trauma surgery, emergency surgery, and surgical critical care.

Dr. Harris: Thank you. Sandra Agazie. Is Miss Agazie with us? Doesn't seem so. Miss Renata Block.

Ms. Block: Good morning. My name is Renata Block. I am a Dermatology Physician Assistant in Chicago, Illinois, practicing in a private practice with advanced dermatology and cosmetic medicine.

Dr. Harris: Thank you. Dr. P. Lamont Bryant.

Dr. Bryant: Good morning. Lamont Bryant. Worldwide Vice President, Regulatory Affairs Ethicon, Johnson & Johnson, and I'm the industry representative.

Dr. Harris: Thank you. Miss Rachel Brummert.

Ms. Brummert: Good morning. I'm Rachel Brummert. I'm with the American Society of Pharmacovigilance, and I will be the consumer representative today.

Dr. Harris: Thank you. Miss Melissa Fisher.

Ms. Fisher: Hi. Yes. Good morning. I'm also a consumer advocate representing several advocacy groups out of the Boston, Massachusetts area.

Dr. Harris: Thank you. Dr. Heather Dean.

Dr. Dean: Hi. My name is Heather Dean and I'm the acting director of the Division for Infection Control and Plastic Surgery Devices.

Dr. Harris: Thank you. Dr. David Krause.

Dr. Krause: Hi. Good morning, everybody. I'm David Krause. I'm the Deputy Office Director for the Office of Surgical and Infection Control Devices, also known as Office of Health Technologies 4. Thank you.

Dr. Harris: Thank you. And Dr. Binita Ashar.

Dr. Ashar: Good morning, everyone. My name is Binita Ashar. I'm a general surgeon and I'm the Director of the Office of Surgery and Infection Control Devices at FDA.

Dr. Harris: Thank you, all. Candace Nalls, the Designated Federal officer for today's General and Plastic Surgery Devices Panel, will make some introductory remarks.

Ms. Nalls: Good morning. I will now read the Conflict of Interest Statement. The Food and Drug Administration, FDA, is convening today's meeting of the General and Plastic Surgery Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representative, all members and consultants of the Panel are special government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C subsection 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C subsection 208, Congress has authorized FDA to grant waivers to special government employees and regular Federal

employees who have financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential conflict of interest.

Related to the discussion of today's meeting, members and consultants of this panel who are special government employees or regular Federal employees have been screened for potential financial conflicts of interest of their own, as well as those imputed them, including those of their spouses and minor children and for purposes of 18 U.S.C subsection 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

For today's agenda in the morning, the panel will discuss and make recommendations on the classification proposal for tissue expanders and accessories, which are currently unclassified preamendments devices to be Class III general controls and premarket approval, and Class II general and special controls and mammary sizers, which are currently unclassified preamendments devices to be Class II general and special controls. In the afternoon on the first day, the panel will discuss and make recommendations on the classification proposals for wound dressings with animal derived materials, absorbable synthetic wound dressings, and hemostatic wound dressings with or without thrombin, which are currently unclassified preamendments devices to be Class II general and special controls.

Based on the agenda for today's meeting and all financial interests reported by the panel members and consultants, a conflict of interest waiver has been issued in accordance with 18 U.S.C subsection 208(b)(3) to Dr. Matthew Bloom. Dr. Bloom owns between $25,001 and $50,000 worth of stock in the affected firm. The waiver allows this individual to participate fully in the panel deliberations. FDA's reasons for issuing the waiver are described in the waiver

documents, which are posted on the FDA's website at www.fda.gov/advisorycommittees. Copies of the waiver may also be obtained by submitting a written request to the agency's Division of Freedom of Information at 5630 Fisher Ln. room 1035 Rockville, Maryland, 20857.

Dr. P. LaMont Bryant is serving as the industry representative acting on behalf of all related industry. Dr. Bryant is employed by Ethicon Inc., a subsidiary of Johnson & Johnson. We would like to recommend members and consultants that if the discussions involved any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and exclusion will be noted for the record. FDA encourages all other participants to advise the panel of any financial relationships they may have with any firms at issue. A copy of this statement will be available for review and will be included as part of the official transcript. Thank you.

For the duration of the General and Plastic Surgery Devices Panel meeting on October 26, 2022, Dr. Deborah Armstrong, Melissa Fisher, and Dr. Andrew Seidman have been appointed to serve as temporary nonvoting members. For the record, Dr. Armstrong and Dr. Seidman serve as consultants to the Oncologic Drugs Advisory Committee at the Center of Drug and Evaluation Research, CDER. Miss Fisher serves as a patient representative consultant for the Oncologic Drugs Advisory Committee in CDER. These individuals are special government employees who have undergone the customary conflict of interest review and have reviewed the materials to be considered at this meeting. The appointments are authorized by Russell Courtney, Director Advisory Committee Oversight and management staff on September 27, 2022.

Before I turn the meeting back over to Dr. Harris, I would like to make a few general

announcements. In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time that you speak. The press contact for today's meeting is Audra Harrison. Thank you very much, Dr. Harris.

Dr. Harris: Thank you. And before we proceed, I have the pleasure of introducing two additional committee members. Each of you would like to just to speak, give your name, your affiliation, and area of expertise. We'll begin with Dr. Alan Matarasso.

Dr. Matarasso: Thank you. I apologize for the delay. I'm caught in weather. My name is Dr. Alan Matarasso. I'm a practicing plastic surgeon in Manhattan, Clinical Professor of Surgery at Northwell Hofstra University, and a past President of the American Society of Plastic Surgeons. Thank you.

Dr. Harris: Thank you. And I would like to also introduce Dr. Stephen Li.

Dr. Li: Good morning. My name is Stephen Li. I'm currently an independent consultant. I have my own private laboratory. My areas of expertise are biomedical materials on bioengineering.

Dr. Harris: Thank you very much. We will proceed with the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the panel to present data, information, or views relevant to the meeting agenda. Ms. Nalls will read the Open Public Hearing disclosure process statement.

Ms. Nalls: Both the Food and Drug Administration, FDA, and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the Open Public Hearing session at the Advisory Committee Meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA

encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it does not preclude you from speaking.

Dr. Harris: Thank you, Ms. Nalls. FDA has received four requests. Each speaker will be given five minutes to present. The first speaker this morning is Ms. Maria Gmitro.

Ms. Gmitro: Good morning. My name is Maria Gmitro. I'm a board certified patient advocate and president and founder of BISA, Breast Implant Safety Alliance. I'm also a patient Patient's Rising delegate and serve on multiple consumer and patient safety organizations. I do not have any financial conflicts of interest to disclose. I also do not have a slide presentation, but we have drafted a short statement and will also post this on our website at BisaNonprofit.org.

When we heard about this public meeting, we reached out to our community and patient network. Due to October being Breast Cancer Awareness Month and the timing to submit feedback was very short, we felt it was more difficult to elicit feedback as many individuals were busy with awareness events. Overall, what we hear from patients is that they feel they were not properly informed and are unaware of which devices were placed in their body. Since expanders and sizers are similar to breast implants, patients should be properly informed of all the risks and potential complications.

In preparation for this meeting, BISA also reviewed the data analyzed by Madris Kinard of Device Events presenting at today's meeting. We plan to link her presentation to our website. Breast implant, tissue expanders and sizers are currently unclassified. However, they are an implanted medical device, which has adverse event reports. We appreciate that the FDA will be classifying these devices. However, we feel a Class III classification is better than a Class II. Especially due to the data coming from adverse event reports. We hear from patients that they often keep the breast implant expanders much longer than expected. Some patients have chosen not to continue with reconstruction and keep an expander in their body. Not sure why this practice is allowed, but it is concerning. Patients should be provided with device tracking information, including the EDI. Some of these devices have also been recalled in the past few years due to a link to lymphoma. What is concerning is that patients are not aware of which type of breast implant expander or sizer was placed. There are cases of BIA ALCL where patients that did not have recalled breast implants. However, they did have recalled expanders and were unaware. According to the medical device reports, patients are reporting systemic systems commonly referred to as Breast Implant Illness. Besides illness, there are also reports of cancer, lymphoma, and carcinoma.

In summary, BISA recommends that these devices receive a classification. However, we believe a Class III would be better than a Class II. Patients receiving these devices should be properly informed of risks and potential complications because they are similar to those of breast implants. Patients should be provided with all device tracking information, including the EDI, and should be encouraged to keep track of this information even after the device has been removed. Tissue expanders should not be used as a permanent implanted device without proper informed consent. The FDA should send a letter to providers to ask them to report cases of

systemic symptoms, Breast Implant Illness, or related cancers. Thank you, FDA, for allowing me to speak this morning.

Dr. Harris: Thank you. Our next public speaker will be Ms. Joan Melendez.

Ms. Melendez: Good morning. Sorry. Having a little difficulty there unmuting myself. Thank you for granting me the opportunity to discuss the importance of classification assignments. I have no financial conflicts of interest. My name is Joan Melendez of Xcelrate UDI and we specialize in parsing the UDI into clinical and financial applications. I humbly request that you please take patient safety considerations and the ability to accurately document and trace mammary sizers tissue and wound dressings when determining the assignment of classification codes.

In my opinion, any medical device used within a surgically cut or naturally formed cavity must be assigned at a minimum a Class II assignment. Medical device codes and classifications identify medical devices as a supply or as an implant, which drives healthcare VRT's, the financial systems, and the EHR's or EMR's, the patient records. Classification drives if clinical documentation can take place in an electronic system. Use of accurate classifications allow the parsing of UDI details that identify medical devices down to the lot or serial number, which then can be used not only to identify adverse events, but may help to prevent harm by allowing the providers and patients to report issues concerning a specific medical device. The use of UDI identifies recalled items correctly and allows patients to be tracked. The lack of classifications or misassignment of classification has resulted in many healthcare system's inability to document and implant a medical device and contact patients in the event of a recall.

As an example, tissue expanders have currently open recalls. How many recall medical

devices are implanted after the recall as a result of lack of communication as a lack of proper classification or UDI assignment? The only way to accurately document, trace, and report adverse events is by utilizing the UDI, which is driven by medical device codes and classification. Please remember that the UDI can help identify if the adverse event was caused as a result of manufacturing of the device or if there was lot specific or cause at the site as being used. The UDI also identifies if the medical device has MRI safety implications for the patient. Use and enforcement of UDI from manufacturing through disposition, which is a use waste recall adverse event or expiration, is imperative in order to communicate that the medical device is safe for patient use.

Use of the UDI is critical to accurately report adverse events during surgical events, as well as post implementation adverse events. How many adverse events were recorded by the surgeon or patient? How many patients are notified of recalls? How are providers able to prevent the use of recall medical devices? Currently, this is done very poorly. Without the EDI, how would patients, providers, and manufacturers know what to report? Accurate medical device coding, classification assignments, and use of UDI is paramount to patient safety. Thank you so very much for letting me speak today.

Dr. Harris: Thank you. Our next public speaker is Dr. Bernard Lee.

Bernard Lee: On behalf of the American Society of Plastic Surgeons and the Plastic Surgery Foundation, thank you for the opportunity to present today. My name is Dr. Bernard Lee and I'm the president of the Plastic Surgery Foundation of ASPS. I am pleased to share with you our perspective on the proposed reclassification of tissue expanders.

As a board certified plastic surgeon who performs breast reconstruction, breast

reconstruction is an important part of the recovery process. We know that breast reconstruction impacts a woman's physical, psychological, and sexual well-being. The Women's Health and Cancer Rights Act of 1998 requires health plans that offer breast cancer coverage to also provide coverage for breast reconstruction, as well as the associated prosthetic devices. More recently in 2015, the ASPS was instrumental in passing the Breast Cancer Patient Education Act. The goal of this legislation was to inform breast cancer patients about the availability and coverage of breast reconstruction and other available alternatives after mastectomy, including prosthetic devices.

Which brings us to today. One of the key devices often used to make breast reconstruction widely possible are tissue expanders. These tissue expanders are temporary empty implants inserted into the chest at the time of mastectomy or even later to help stretch the skin. Over a period of weeks, they are gradually filled with saline or air. The tissue expander creates the room needed for the permanent breast implant to be inserted during a second surgery. These devices are incredibly important as we fulfill the promise of the Women's Health and Cancer Rights Act.

Tissue expanders enable surgeons to provide wide access to breast reconstruction. According to recent ASPS procedural statistics, tissue expander and implant-based reconstruction constitutes approximately 60-65% of all breast reconstructions in the United States. The literature demonstrates the surgery is safe, cost effective, reliable, and able to be performed in women with a wide variety of comorbid conditions. ASPS/PSF does support efforts by the FDA to improve the regulatory oversight of tissue expanders used in breast reconstruction.

We believe that tissue expander devices offer important benefits and are vital to ensuring

access to timely, cost-effective, and safe breast reconstruction for thousands of women. A wealth of data in the literature and from the manufacturers support the safe and effective use of tissue expanders in breast reconstruction. Because these devices have a long-standing use and have a well-documented body of evidence behind them, the ASPS/PSF urges that any change in regulatory status be balanced with a vital need to maintain access to these devices and provide timely care to women after mastectomy.

As a society, we support all appropriate pathways to provide the evidence needed to support these devices in a new classification status. What is one way we can help move forward then? The Plastic Surgery Foundation's suite of registries, the Plastic Surgery Registries Network, the PSRN, has been actively collecting data on plastic surgery procedures, devices, and outcomes since 2002. We have worked collaboratively with the FDA on the development of both a PROFILE registry designed in response to the reports of anaplastic large cell lymphoma with women with breast implants. And the National Breast Implant Registry, NBIR, which is currently designed to capture information on all breast implant procedures and subsequent removal and replacements. The NBIR was formally launched in 2018 after a collaboration between the PSF, the FDA, and breast implant manufacturers.

Born out of the 2011 BIA-ALCL safety signal, the PSF worked closely with the FDA and breast implant manufacturers to develop the National Breast Implant Registry. Since that time, data on nearly 70,000 breast implant procedures have been collected by over 1,400 registered practices. The NBIR serves as an infrastructure for breast implant manufacturers to collect device tracking data from surgeons. This includes collecting patient contact information and device specific information in the event of a recall. In addition to device and patient contact

information, the NBIR collects patient medical history, procedural information, and reasons for a reoperation. The specific device information comes from the surgeons scanning the unique device identifier, the UDI barcode, which then pulls that information directly from the FDA's GUDID database.

Like the FDA, the PSF is committed to collecting real-world data. Real-world data relates to patient health status or healthcare delivery and can be collected from a source like the PSF's NBIR registry. As has been noted by the FDA in its guidance document for industry and FDA staff on the use of real-world evidence and regulatory decision-making for medical devices, real-world data has advantages. Large amounts of timely data is available at a reasonable cost and is representative of the real-world practice of medicine. In considering the kind of data the FDA will need to make regulatory decisions should tissue expanders be reclassified, the PSF believes that we can effectively partner with the agency to ensure NBIR's data collection for tissue expanders is maximally relevant and reliable and able to provide clinically meaningful outcomes and support regulatory decision-making. We have a robust infrastructure already in place to collect device information through the NBIR and we have already started work to open the NBIR to collect device information on expanders and sizers. We can leverage this infrastructure and collect the same device information, allowing the information to be coded as an expander versus an implant. We anticipate this functionality will be available before the end of the year so that the NBIR can continue to be the most robust source of breast implanted device data.

We are committed to working with the FDA and manufacturers to ensure your needs for robust, reliable, and relevant real world data are met, and most importantly, we will do our part to ensure access to these critical devices for our patients. On behalf of the ASPS and the PSF,

thank you for the opportunity to present today.

Madris Kinard: Hi. My name is Madris Kinard and today I'm here to talk about tissue expanders. I previously worked for the FDA in the Office of Post-market Surveillance on the MAUDE data, which is essentially the adverse event reporting system. I'm also a member of the Breast Implant Safety Alliance, but nobody has paid me to present today.

Tissue expanders are often used prior to breast implants in mastectomy patients. Through September 30, 2022, there have been over 7,000 reports and a majority of these were injury reports. The timeline for these reports that have been received by the FDA is current through the end of September. Here you can see that there were different types of reports being used from 1996-2019. Those reports are now available. Since the end of that reporting type, however, the implant reports have spiked for the tissue expanders. One thing to note is that the ASR's, which are those reports I'm pointing out with the arrows, do not contain a narrative, so it's difficult to understand what happened to a patient. Typically, only 15% of reports to MAUDE are from physicians and tissue expander reports it's 31%. I think that's something that's important for the FDA to understand. Here I've noted the patient problems that are associated with tissue expanders and all of the arrows are pointing to issues that also affect patients with breast implants. The FDA recognizes breast implant illness, but yet there is still no code for it. These are the symptoms that are listed as breast implant illness symptoms. This is on the FDA page as well.

I'm going to back up two slides again and show you that all of these reports with these arrows are similar to those with the breast implant illness device problems. There is currently no patient problem code for breast implant illness, yet we see it in breast implant and tissue

expanders. We also see reports of cancer, lymphoma, carcinoma, and ALCL in tissue expanders. Patients receiving tissue expanders need to be informed that the risks are similar to those from breast implants. This is the narrative search on some of the reports on the MAUDE database. So, these are adverse events for tissue expanders. Here you can see that we have both symptoms of ALCL, seroma, lymphoma in the first report, and in the second report there are breast implant illness symptoms.

So, what can the FDA do to inform patients and care providers? The FDA should send a letter to all types of care providers to ask them to report cases of BII and different types of cancer. Breast implant illness needs a unique ICD 10 code and patient problem code. The patient problem codes for cancer need to be more specific, such as carcinoma. Tissue expanders should require informed consent similar to that required for breast implants. Tissue expanders should not be used as a permanent device without this informed consent. Those are the recommendations I'm making to the FDA today. If you need to reach me, my contact information is included in the slides. Thank you very much for your time.

Dr. Harris: Thank you. So, do any of the panel members have any questions for the Open Public Hearing speakers? First question: Miss Rachel Brummert.

Ms. Brummert: I have a question for Dr. Bernard Lee if he's still on the call.

Dr. Glasberg: This is Dr. Scott Glasberg. Dr. Lee is not available, so I'm taking his questions for him representing ASPS and the Foundation.

Ms. Brummert: Okay. He mentioned a national registry. Do breast implant patients have access to that database?

Dr. Glasberg: So, the National Breast Implant Registry is a joint venture between the

foundation and the FDA and so there's not open access to it at the moment. However, there is a motion in place to allow patients reporting into a NBIR in the near future.

Ms. Brummert: Okay. Thank you.

Dr. Harris: Next question. Ms. Renata Block.

Ms. Block: Hello. This is Renata Block. Thank you for your presentations today. They were very informative. My question to all of you is what are your thoughts about the mammary sizer as far as a class? Do you feel that it is as sufficient to be a Class II or III and why?

Ms. Kinard: This is Madris Kinard. I think from the perspective of how breast implants were up classed to Class III that it would be a good recommendation since the breast implant or the tissue expanders have similar outcomes. That would be my recommendation.

Ms. Melendez: Hi. This is Joan Melendez. Great question. Thank you for that. It's one of those, you know, what is the use? Is it implanted? It's used during surgical cases, the sizers, but then they are disposed of, you know, within that surgical case. The most important thing is, in my opinion, is to be able to really track it not as a supply and that's what it will be, you know, if anything lower than Class II. It would be nice to have all of them as a Class III, but since it's not an implantable device, it really doesn't qualify for a Class III. Class II would be perfect. Thank you so much.

Dr. Glasberg: If I could chime in and echo both sentiments. I mean, Class II is, as far for sizers, it's more than enough. We can do many things in surgery that go in and out of the wound with all different types of devices, instruments, and whatnot. A sizer is really just something that's put in, adjusts for that to adjust size, and ends up immediately removed. So, it wouldn't even fall into the category of implantable device. It falls more in the category of instrumentation

or devices that are just used in the wound during surgery.

Dr. Harris: Just like to remind all the speakers to please state your name for --

Dr. Glasberg: I apologize.

Dr. Harris: No apology necessary. Just a little reminder. To know the comments regarding that line of questioning, I have a question from Dr. Li.

Dr. Li: Yes. Thank you. We've heard from about two databases. The NBIR and the MDR, but they are very different sizes and are very different methods of data collection. Has there been any comparison, for instance, of the adverse events or types of adverse events or differences between the results of the NBIR and the MDR reports?

Dr. Glasberg: So, this is Dr. Scot Glasberg again. I can take that. So, there is continual evaluation of the data. In fact, there's quarterly reports out of the NBIR. So, they are assessed and compared on a continual basis. In fact, in terms of the PROFILE registry, we do a continual assessment to try to determine and make sure there's no overlap in cases so we get an accurate count of cases at the ALCL. The benefit actually of both is that, as you can imagine, the MBR reports get certain information on certain cases and PROFILE may get other data on different cases, but also data on the same cases. So, the ability to look at both set data sets gets us more information in the long run.

Ms. Kinard: Yeah. So, the FDA -- or I'm sorry the NBIR registries are primarily getting data to my understanding from plastic surgeons and MDR's can come from any specialty area. So, if you have systemic issues with the device, then those registries aren't necessarily being used by the physicians that are seeing those patients. And that was one of the reasons I even recommended pushing or sending out a letter to all types of physicians to report these problems

to the FDA, and when I say that I did mean by the MDR. Some physicians feel that if they're reporting to a registry that it's the same as reporting to the FDA and that's not necessarily the case. The registry data does not get fed to the FDA in any uniform manner.

Ms. Melendez: And if I could add onto Madris's comment. You know, the NBIR --

Dr. Harris: Who is speaking?

Ms. Melendez: I'm sorry. I'm sorry. Joan Melendez. I apologize.

Dr. Harris: Thank you.

Ms. Melendez: You know, it's a closed network, so only those members, those people who are members, have access to these reports. So, you know, and if the member is only reporting the adverse event to their registry, then they are failing to report it to the FDA. Most surgeons don't even go that far. They report it to the manufacturer, who then reports it to the FDA. So, when are we really getting accurate notification? It needs to happen more real-time. Scanning and documentation of that UDI at the point of care is so important and the classification will help drive that. So, I appreciate your time.

Dr. Harris: Thank you. We have a question or comment from Dr. Seidman.

Dr. Seidman: Thank you. This is Dr. Andrew Seidman. I'm a Breast Medical Oncologist. I just want to thank the advocates for their comments and the presenters for their very clear presentations. This is not an area of medicine that I've thought deeply about until the last few weeks. My question is actually probably to Dr. Bernard Lee and the focus is on trying to tease out if possible the contribution of the tissue expander versus the implant to a plastic large cell lymphoma. And I'm wondering if the NBIR data set or any real-world data could be helpful

in identifying patients who perhaps had tissue expanders in for up to six months, but who never had a permanent implant for various reasons. Patient choice, device failure, infection, etc. as one way to get at this. And then also patients who underwent direct implantation of an implant without a tissue expander. Is there any existing data to help tease out the contribution of the tissue expander to ALCL from that kind of analysis?

Dr. Glasberg: Thank you for that question. This is Dr. Scot Glasberg again. I think the answer is an unequivocal yes and that, you know, one of the things that are difficult with BIA-ALCL is we generally know the last implant that's removed from the patient, but we don't always have the history of prior implants that were used. So, the issue of texture versus smooth is one that comes up all the time. There are cases in the literature even of women who have developed the BIA-ALCL after a textured tissue expander followed by what is believed only smooth implants. The other thing that the PROFILE registry and the NBIR allows to do is follow patients beyond their initial treatment should they have another issue later on with or without another implant or with nothing in place and there are cases of BIA-ALCL that have been reported with, again, with textured tissue expanders as part of the history. So, to answer your question is yes, we can call that data out of what we know from both the PROFILE registry and NBIR.

Dr. Seidman: Thank you.

Dr. Harris: Thank you. Next question from Dr. DeLong. You are on mute, Dr. DeLong.

Dr. DeLong: Dr. Seidman was kind of asking in the direction that I was thinking. So, one of the questions was are there any cases of ALCL that we can directly attribute to the tissue

expanders and they had no following implant and it seems like the patient population it might be most illustrative for that is sometimes we put in tissue expanders to preserve the skin envelope and then go back and do a flap. And so, have we ever observed a BIA-ALCL case in one of those patients? I know Dr. McCarthy is on here and she's the PI of PROFILE.

And the second piece is looking at the NBIR. The advantage of a Class III designation is it allows more robust clinical studies in the premarket space, but BIA-ALCL has a latency period of 8-10 years. So, doing a big clinical study for six months isn't necessarily going to tell you anything in the free market space. So, parsing out or, you know, identifying an association between tissue expander types and ALCL is really going to happen in the post-market registry space. And so, is NBIR set up, as I recall, it basically would track patients from the first time they got an implant placed and then any time they got an implant switched after that. Does it track tissue expanders? Is it possible to, you know, adjust the NBIR in such a way that we can actually develop data for BII or ALCL for tissues expander patients? And then, you know, I think the PROFILE registry is going to be of vital importance for any of those kinds of concerns.

Dr. Glasberg: It's Dr. Scot Glasberg again. I don't know if Dr. McCarthy -- I know she had her hand up if she wanted to address this or if she wanted me to do it. Go ahead if you want.

Dr. McCarthy: Thanks, Dr. Glasberg. Yes. This is Colleen McCarthy and I'm the Principal Investigator at the PROFILE Registry. So, Dr. Seidman, to answer your question directly, notably the PROFILE registry collects physician reported cases of breast implant associated ALCL. We have over 400 reports of ALCL in the United States. We have granular level detail on nearly 300 of these cases. Approximately 50% of cases occurred after cosmetic breast implantation, so no tissue expander was placed. The other 50% occurred in patients who

had post mastectomy breast reconstruction using implants or tissue expander and implants. Approximately 90% of this cohort, reconstructive cohort, had a tissue expander or two tissue expanders placed. In one case, a patient had a tissue expander history of multiple current infections. This tissue expander was left in place for over a year and reportedly developed ALCL. There are no cases, to answer your question, Dr. DeLong, that PROFILE is aware of in a patient who had a tissue expander, orthologous tissue reconstruction, or what we call a flap, and then developed the disease.

Dr. Glasberg: It's Dr. Scot Glasberg, and if I could just add one more thing that I think is worth reiterating. In Dr. Li's comments, he mentioned the fact that the foundation is committed to expanding the NBIR to include now tissue expander cases from that point forward. Not just implant cases. That capability is easily adjusted. It should also be noted and worth mentioning since the topic's come up that we just received IRB approval for the PROFILE Registry to expand its ability to now not only take up cases related to BIA-ALCL, but also cases related to the Safety Advisory from FDA recently on breast implant associated squamous cell carcinoma and B cell lymphomas as well. So, we are able, given the robust nature of our infrastructure, to routinely adjust as issues come up and allow our real-time data to enhance itself and follow long-term. Thank you.

Dr. Harris: Thank you. And, Dr. McCarthy, your hand is still up so you have an additional comment or question? No. Dr. Armstrong.

Dr. Armstrong: Thank you. This is Deb Armstrong. I wonder if either the FDA or the other registries have been tracking information on whether the patients received chemotherapy or radiation therapy since both of these treatment modalities are associated with

secondary or treatment-related malignancies, and although these are not typically ALCL, this I think would be important information to know certainly if the cosmetic versus breast cancer ones you would be able to know that those patients did not get treatment, you know, chemotherapy or radiation, but whether the use of radiation or chemotherapy is being tracked with these and whether there's any data to suggest that either of these are associated with an increased risk of the ALCL.

Dr. Glasberg: This is Dr. Scott Glasberg again. So, that is a standard part of the data set for both NBIR and the PROFILE Registry. Similar to PROFILE registry, it is drafted throughout the course, including the treatment after the diagnosis to assess that as well. So, those are significant data points within CRS.

Dr. Harris: Thank you. Dr. Pusic.

Dr. Pusic: Morning again. Dr. Andrea Pusic. And as previously mentioned, I am co-chair of the U.S. National Breast Implant Registry and have been leading the registry to its development to its inception. Just a few points. I think Dr. Glassberg has clarified some things for us as well, but just to clarify a few points in terms of both strengths and the weaknesses of the NBIR. As the NBIR, the main adverse event reporting is triggered by reoperation, which I think is in many ways a limitation in the sense that events could be happening that we are not aware of and then lead to explanation or to reoperation. That said, we are working hard to incorporate patient reporting, patient reported outcomes, symptom reporting, and the reporting of symptoms potentially associated with breast implant illness into the registry. So, that's kind of our next big step that we will be taking.

Another I would say limitation of the registry is to support Ms. Kinard's comment is it is

the surgeons, plastic surgeons who are the implanting devices that are the primary reporters. So, there is a potential loss of reporting if a patient presents to, say, their rheumatologist. That said, we do accept reporting from non-plastic surgeons. So, implanting surgeons that could be in another subspecialty another area. So, we reach out so this is not limited to surgeons who are part of the American Society of Plastic Surgeons, which is a strength.

So, I would just say I think that the NBIR has been an important contribution. We are growing exponentially. There are numbers rising tremendously. There is great commitment by our ASPS members to report this data, and has been mentioned, we are actively already incorporating the reporting of tissue expanders into the registry, which would be an additional safety step and would allow us to -- I think Dr. DeLong mentioned is the important is the NBIR gives us unique opportunity to follow patients in the long-term and postapproval in the postapproval states and be able to track complications many years out, which I think is really of interest terms of patient safety.

Dr. Harris: Thank you. Are there any other questions or comments? Great. So, I now pronounce the Open Public Hearing to be officially closed. I would like to invite the FDA to start their first presentation and I would like to remind the public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair. FDA, you may now begin your presentation.

Dr. Wilder: Hello. My name is Frances Wilder and I am a regulatory advisor within CDRH's Office of Product Evaluation and Quality. I will be providing you with a high-level overview of the medical device classification process, which formed the basis for our discussion during this panel meeting.

The purpose of this panel meeting is to discuss the classification of devices that currently remain unclassified. Specifically, for 10 pre-amendments and classified device types, the panel will be asked to provide input to the FDA on the appropriate classification for each device type. FDA categorizes medical devices into three classes based on the regulatory controls necessary to mitigate the risks associated with the device type. Class I devices are only subject to general controls. Class II devices are subject to both general and special controls. And Class III devices are subject to general controls and premarket approval. These regulatory controls will be discussed in greater detail in the following slides. The important takeaway here is that a device should be placed in the lowest class whose level of control provides a reasonable assurance of safety and effectiveness.

Now, we will go into a bit more detail about each of the classes. Again, Class I devices are those devices for which general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device. General controls are basic requirements that apply to all medical devices and are outlined in the Federal Food, Drug, and Cosmetic Act. Some examples of general controls include meeting establishment registration and device listing requirements, following good manufacturing practices, adhering to recordkeeping and reporting requirements, and ensuring that devices are not misbranded or adulterated. Most Class I devices do not require FDA premarket review prior to being marketed. On the right-hand side of the slide, you can see a few examples of Class I devices, which include simple gauze wound dressings, manual surgical instruments for general use, and introduction drainage catheters. There is also an alternative pathway to determine that a device is Class I. Class I devices could also be devices that cannot be classified into Class III because they are not life-sustaining, life supporting, or of substantial importance in preventing impairment of human health. And they do not present a potential and

reasonable risk of illness or injury. And these devices cannot be classified into Class II because insufficient information exists to establish special controls to provide a reasonable assurance of safety and effectiveness.

Class II devices are those devices which cannot be classified into Class I because general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness of the device. And for which there is sufficient information to establish special controls to provide such assurance. There are many types of special controls, but some examples include performance testing, sterilization validation, and device specific labeling requirements. These special controls, in combination with the general controls previously described, provide a reasonable assurance of safety and effectiveness for Class II devices. Examples of Class II devices include surgical sutures, negative pressure wound therapy devices, and laser surgical instruments for general and plastic surgery use. Typically, Class II devices require a premarket notification or commonly referred to as a 510(k) prior to being marketed in the US. Within these 510(k) case submissions, companies must also provide evidence demonstrating how the special controls for the specific device type are met.

Class III devices are those which cannot be classified into Class II because insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device. And the devices are life-sustaining or life supporting or are of substantial importance in preventing impairment of human health or they present a potential unreasonable risk of illness or injury. Class III devices typically require premarket approval through a premarket approval application, or PMA, prior to being marketed. Examples of Class III devices include breast implants, dermal implants for aesthetic

use, and absorbable hemostatic agents.

Here you can see a flowchart which walks through the general decision-making process for device classification. We start with determining whether general controls are sufficient to provide reasonable assurance of safety and effectiveness. And if so, the device can be appropriately regulated in Class I. If not, we ask whether there is sufficient information that allows us to develop special controls. If so, the device can be appropriately regulated in Class II. If not, then it would be Class III if the device is life supporting or life-sustaining or if it is of substantial importance in preventing impairment of human health or if it presents a potential and reasonable risk of illness or injury. If the device is not life supporting or life-sustaining or of substantial importance in preventing impairment of human health and does not present a potential and reasonable risk of illness or injury, then we end up back at Class I designation.

Now that we have discussed the general device classification scheme, we will move onto the classification process for the pre-amendments unclassified device types, which were the focus of this panel meeting. For those who are unfamiliar, a pre-amendments device refers to a device type, which was introduced into interstate commerce prior to May 28, 1976, or the date of enactment of the medical device amendments to the Federal Food, Drug, and Cosmetic Act. An unclassified device is a pre-amendments device, which was not classified by the original classification panels. Therefore, no classification regulation currently exists for these devices.

This brings us to the purpose of this panel meeting, which is to formally classify these unclassified devices. Please note that while these devices are not classified, they currently have to be cleared through the 510(k) process prior to being marketed. These pre-amendments unclassified devices will be classified once the FDA has taken the following steps. First, FDA

will solicit input and a recommendation from the device classification panel, which is the purpose of this meeting. After this meeting, FDA will publish the panel's recommendation for comment, along with a proposed rule outlining FDA's proposed classification for the device. Finally, after taking into account public comments, the FDA will publish a final rule classifying the device.

During this panel meeting, we ask the panel to provide input on the classification of these unclassified device types and whether each should be classified into Class III, Class II, or Class I. The panel input should include an identification of the risks to health presented by each device type and a discussion of whether the device is life supporting, life-sustaining, or of substantial importance in preventing impairment of human health or if the device presents a potential and reasonable risk of illness or injury. The panel will be asked to discuss whether general controls alone are sufficient to provide reasonable assurance of safety and effectiveness for each device type, and if not, whether sufficient information exists to develop special controls and what those special controls should be to provide a reasonable assurance of safety and effectiveness for the device type.

Following this panel meeting, the FDA will consider all available evidence, which includes the input received from this panel and the public. The FDA will then publish a proposed rule in the Federal Register proposing classification of these device types and seeking public comment on the proposal. Finally, FDA will issue a final rule identifying the appropriate class. If FDA determines that the device can be appropriately regulated as Class I or Class II devices, these devices may continue to be marketed. If, however, FDA determines that they fall into a Class III designation, a separate call for PMA's will also be published. Existing devices may

remain on the market until a specified date, at which point a PMA must be submitted in order to continue marketing the device. If this PMA is not approved, the existing devices would be considered misbranded and must be removed from commercial distribution. I hope that this has provided you with sufficient background information to set the stage for the forthcoming discussions. Thank you for your time and attention.

Dr. Harris: Does any member of the panel have any clarifying questions for the FDA? Dr. DeLong.

Dr. DeLong: I have two quick questions. One, we're about to discuss a classification for LCJ, but the PQN tissue expanders, which are common dioxide inflatable tissue expanders that have historically been Class II. Is there any plan to readdress their classification? My second question are what are the device tracking capabilities for Class III versus Class II? Is there any availability to do post-market tracking for Class II devices?

Dr. Harris: Who from FDA would like to respond to those questions?

Dr. Dean: I can say something. This is Heather Dean. So, for the purposes of this panel, we are focusing only on these pre-amendments devices for classification. There are no plans to address any other product codes in this panel. As for tracking, you know, all devices are tracked post-market through our MDR systems. We do have additional ability to track those that are Class III of course through annual reports from the companies. Does that answer your question?

Dr. Harris: Dr. DeLong?

Dr. DeLong: Sorry. I was getting myself off mute. But in terms of the like, unique device identifiers, I know some of the in the Open Public Hearing there was concern that with

the recalls some patients may not be informed if they had a specific device type. Do you have any capabilities to have that level of tracking with a Class II designation?

Dr. Dean: I believe that all even Class II devices are required to have UDI at this point. You know, we do not receive the same type of information that we receive as with the annual report for PMAs, but users should be able to report which devices they have when reporting to us for MDRs.

Dr. DeLong: Thank you.

Dr. Harris: Thank you. Dr. Seidman?

Dr. Seidman: Yes. This is Andrew Seidman. I just wanted to know how long manufacturers and marketers will have to submit a PMA if tissue expanders are, indeed, designated Class III? The spirit of the question just is in terms of having access. I guess that's a question for somebody from the FDA. The turnaround time that manufacturers will have to submit a post manufacturing approval application if tissue expanders are designated Class III.

Dr. Dean: So, this is Heather Dean. Generally, there is quite a bit of time. At least a year for sponsors to put in their PMA's. It will take some time for us, as was explained, to put out our proposal rule and gather public input and then finalize the rule. So, in short, these devices, existing devices will remain on the market and will have some time before they need to submit a PMA. And we will put out a call for those PMA's, you know, if and when appropriate.

Dr. Harris: Thank you. Dr. Armstrong?

Dr. Armstrong: Hi. This is Deb Armstrong. I wanted to know if there's any -- I realize that this class preceded this 1976 FDA working group, but there clearly have been devices

that have been developed and introduced into the market since then. Have any of those actually gone through PMA or is the entire group of tissue expanders none of them have gone through a PMA?

Dr. Dean: I believe they've all gone through the 510(k) process since 1976. David, you can correct me. Dr. Krause, you can correct me if I'm wrong.

Dr. Krause: Yeah. Hi. This is David Krause. There was one tissue expander that went through the de novo process. That's the one that Mike DeLong alluded to. The one that's filled with air, carbon dioxide -- I'm not sure which one it is right now. I forget. But it is inflated using either air or carbon dioxide. The other part of Mike's question was tracking. Mike, we can use -- we can track Class II devices in the way that we track Class III devices, yes. That answers that question.

Dr. DeLong: Great. Thank you. [multiple speakers]

Dr. Armstrong: I apologize. I guess part of my question was will every tissue expander currently available have to go through this process if it gets changed to a three or are there some that can still be used and will not have to go through the PMA process?

Dr. Dean: If those tissue expanders intended for use in the breast are up classified to Class III, they will be on the market for now, but at some point we will put out a notice to continue to be marketed in the U.S. they will require a PMA.

Dr. DeLong: So, my question was sort of related to the expander that David Krause was just talking about.

Dr. Harris: So, who is speaking?

Dr. DeLong: Sorry. This is Mike DeLong. So, with a PBQ, these inflatable expanders, which are arguably more complex than the saline inflated expanders, but they remain Class II 510K while, you know, LCJ goes to Class III.

Dr. Dean: I will defer to Dr. Krause on that, but my understanding is we are not looking at any other product codes, other than these preamendment devices. Especially in this panel.

Dr. Krause: Right. This is David Krause. That is a topic that we would have to think about later at this point. We are not addressing that here, so I can't really conjecture what we are going to do. Somebody -- you know, patients or companies or anyone is free to submit a citizen's petition requesting that we up classify, but we are not discussing that here, so I can't tell you.

Dr. Harris: Thank you. Dr. Pusic.

Dr. Pusic: Thank you. Andrea Pusic. My question was the same as Dr. Seidman's that I would -- I just -- I'll speak again regarding just to emphasize the importance of that question. So, while I'm very supportive of this change for tissue expanders, I'm also aware of the very long history of the use of tissue expanders safely in the majority of patients. These are breast cancer patients who are often put on a tight timeline in terms of other treatments and access is going to be critically important. And so, while I support this change in the interest of safety, I also would not want to see a gap where we have problems with access to tissue expanders. So, I just think access to tissue expanders for our breast cancer patients would be of extreme importance and just the concern that industry have sufficient time to be able to respond to these changes and have approval of tissue expanders in the new classification.

Dr. Dean: We agree and that is something that we would look at and make sure that

there is sufficient time to ensure that devices are available to patients.

Dr. Harris: Ms. Fisher.

Ms. Fisher: Thank you. Sorry. I apologize. I misidentified myself. I'm actually a patient advocate. So, a lot of this is certainly important and I think the concern is what would our options be if they certainly were reduced and most of these had to go through the PMA process and the options became a lot more strained to us where the patients themselves I think aren't as knowledgeable or as informed to a lot of what would be going on and it's something that we would be able to come together and petition and so forth, but that's not really at the top of their mind, particularly if they are an oncology patient. So, I think that would be a big problem and a concern that would need to be addressed from a patient perspective is one concern. And the other -- and maybe this comes up later, but I know the difference between the timeframe of being, you know, in the body for such a short period of time versus a real implant and being able to tell whether this is actually something that is the cause of this being a disease later on or whether this implant is something that's hard for me to get my arms wrapped around from that perspective. I'd like to just hear a little bit more comment about that, but maybe that can happen later.

Dr. Harris: Okay. So, I would just like to step in for just a quick minute. I may have misled the panel. What we are really talking about right now are any clarifying questions regarding the classification process. For example, the excellent comments that were just made we will have an opportunity to discuss after the FDA presents on that specific topic. So, if there are any other questions about the classification process, we should address those now and then we will get to these other very important issues just a little later.

Ms. Fisher: Okay. My apologies.

Dr. Harris: No. No apologies necessary. Probably by mistake in inadequate clarification or instructions. Miss Block.

Ms. Block: Thank you for that clarification. My question is previous history of these classification processes and changing classifications and really limiting other companies -- oh, gosh. Let me take that back. I know we are focusing on one type of product code. I understand that and I understand there are other product codes out there. My question to the FDA is previous history of these changes of classifications from or designation. Did it limit the use of products if they were changed from one class to another or designated into a different class? And I know it's kind of a roundabout question, but it really determines on the classification system and the future of these products. So, I guess maybe a history of a similar situation that was presented in the past and the outcome.

Dr. Dean: So, I know of devices that have been up classified. As I mentioned, there is a process that takes some time and devices stay on the market and then there is a call for PMAs. We do make sure that there are plenty of opportunities for these devices and the variety of devices to stay on the market. Appropriate, of course, with the classification we want to make sure that we are doing what we need to to make sure that the devices on the market are safe and effective for patients. I'm trying to think of specific examples. I know that there was one from the neural stimulation oncology team that has moved to Class III and they are working on that process right now of bringing in PMA's and as far as I know there is still a variety of devices on the market and they are ensuring that. So, I would trust in that process.

Dr. Harris: Thank you. So, I think now we have time for another presentation from the FDA on the tissue expander and accessories.

Ms. Ki: Good morning. My name is Tajanay Ki and I'm a lead reviewer in the Division of Infection Control and Plastic Surgery Devices within the Office of Surgical and Infection Control Devices in CDRH's Office of Product Evaluation and Quality. Today, I will be presenting information regarding our effort to classify tissue expanders and accessories regulated for product code LCJ. These devices are currently unclassified and we are looking for your thoughts and recommendations on the appropriate regulatory classification for these devices.

This is the outline for my presentation. These are the items that we will be discussing today. Tissue expanders and accessories are intended for temporary subcutaneous or sub muscular implantation to develop surgical flaps or additional tissue coverage in a variety of surgical applications, such as breast reconstruction following mastectomy, treatment of underdeveloped breasts, scar revision, and treatment of tissue deformities or injuries. Tissue expanders are intended for temporary implantation not to exceed six months. Tissue expanders can be used in various anatomical locations, including breast, head, neck, calf, and others. Each tissue expander is composed of an inflatable silicone elastomer outer shell with an injection port. Tissue expanders are available in many different sizes, volume ranges, dimensions, and surface texture, including smooth and textured. Tissue expanders are gradually filled with normal physiological saline through the injection port. Tissue expanders also have accessories, such as port detectors, fluid dispensing systems, needle infusion sets, external fill ports, and syringe assists.

The indications for use identifies the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended. The indications for use for tissue expanders specific to the breast include breast

reconstruction after mastectomy or other trauma, correction or treatment of an underdeveloped breast, treatment of soft tissue deformities, and combined chest wall and breast deformities. The indications for use for tissue expanders specific to non-breast include limb reconstruction, scar revision, tissue defect procedures including congenital deformities, cosmetic defects, correction of burn sequelae, baldness surgery, facial tumors, moles, and other skin blemishes, expand tissue to aid in the primary closure of defects, such as nevi and lesions, and to recruit additional tissue within a designed adjacent flap by expansion. Tattoo and other anomaly removal, facial reconstruction and treatment, and decubitus ulcer.

Some tissue expanders include indications for breast and nonbreast use. The accessory to tissue expanders have been cleared for detecting the location of the remote injection port or integral injection port and assisting the clinician in delivery of sterile saline into the surgically placed subdermal temporary removable tissue expander. Tissue expanders and accessories are a preamendment unclassified device type. This means that this device type was marketed prior to the Medical Device Limits Act of 1976. It was not classified by the original classification panels. Currently these devices are being regulated through the 510(k) pathway and are cleared for marketing if their intended use and technological characteristics are substantially equivalent to a legally marketed predicate device. Since these devices are unclassified, there is no regulation associated with the LCJ product code. To date, a total of 48 510(k) have been cleared through the premarket notification 510K pathway under the tissue expander product code LCJ, including 42 expanders and six accessories. Please refer to section 2 of the executive summary for a complete list of clear devices under product code LCJ.

On August 26, 2005, FDA presented information on tissue expanders, including certain

risks of use and potential risk mitigation measures at the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee. The purpose of this meeting was to discuss the classification of tissue expanders among other unclassified preamendment devices. The identified risks included skin trauma, device failure, infection, adverse tissue reaction, and pain. The mitigation measures recommended included labeling, preclinical testing, sterility, and biocompatibility. Following the discussion, the panel recommended unanimously that the agency classify tissue expanders as Class II medical devices with special controls and requiring 510(k) premarket notification.

Since 2005, there have been new developments in implant-based breast reconstruction, including new knowledge of potential risks to health. This includes discussions around the risk of developing breast implant associated anaplastic large cell lymphoma or BIA-ALCL and breast implant illness, or BII. Also in 2019, the FDA requested that Allergen, the manufacturer of a specific type of textured implant, recalls specific models of its textured breast implants and textured tissue expanders from the U.S. market due to the risk of BIA-ALCL. Therefore, considering the significant developments with respect to new risks related to the use of breast implants and tissue expanders intended for breast reconstruction, FDA is convening this classification panel to discuss the current landscape of product technology, indications for use, safety and effectiveness, and risks to health on which to base classification of tissue expanders, which can be used in the breast, as well as other anatomical locations.

Tissue expansion is a procedure used in surgeries when there is not enough skin or tissue coverage to achieve the intended outcome. Tissue expanders are intended for temporary subcutaneous or submuscular implantation near the area to be repaired and then gradually filled

with saline to develop surgical flaps over additional tissue coverage over time. Tissue expanders may also be used in other anatomical regions, such as the head, neck, and calf. The image on the slide represents a typical tissue placement in the breast after a mastectomy. Patient outcomes following tissue expansion may be based on a combination of clinical parameters, including the amount of skin or tissue stretched, the ability of the tissue to accommodate an implant, and tissue necrosis. Alternatives for all expander use can include no reconstruction, external prosthesis, autologous tissue reconstruction, or not using a tissue expander. For tissue expanders typically used in the breast, a direct breast implant is in additional alternative treatment.

We conducted a literature review to identify any published information between April 1, 2005 and April 1, 2022, regarding the safety of tissue expanders. Searches were limited to publications in English and excluded laboratory studies, animal studies, economic and cost-effectiveness analyses, nonclinical trials, case series, and case reports. The search yielded 2202 initial literature references. Following a review of the titles and abstracts, a total of 357 articles remained for full text review. Of these, 18 articles were determined to be relevant to the safety and/or effectiveness of tissue expanders. The number of each excluded criterium is also summarized in the flow diagram. The 18 selected studies consisted of 10 retrospective studies, five nonrandomized prospective studies, two systematic literature reviews, and one randomized control study. Of the 18 included studies, 17 studies examined the use of tissue expanders in the breast and one study examined tissue expanders in dentistry. Note that because tissue expanders have not been cleared for use in dental areas, the single study that examined tissue expanders in dentistry was excluded from the search results for the analysis. Therefore, 17 literature articles are reviewed for the purposes of this literature search on tissue expanders.

The majority of the included studies assessing tissue expanders for use in the breast reported complications. The table on this slide lists the top reported outcomes that were reported by the 17 studies assessing tissue expanders for use of the breast. The table showing a full listing of outcomes is listed in section 5 of the executive summary. Some of the top reported outcomes include infection, skin trauma, necrosis, seroma, device failure, and hematoma, amongst others. In the 17 articles used, tissue expanders were used for expansion. However, the articles did not describe the overall effectiveness of the tissue expander. In summary, no articles in our literature review provided information on tissue expander use in the nonbreast.

There were also limitations of literature review. 10 of the 17 articles included studies used a retrospective study design. A major limitation was that the search excluded case report studies. Case-control studies can be known to be prone to several biases as patient and provider characteristics may not be balanced across study arms. Study funding source, which is a potential source of bias, was not reported in 11 studies, was reported as not funded in two studies and the remaining four studies were funded by nonbiased sources. Overall, the systematic literature search supports a conclusion that there are additional risks associated with the use of tissue expanders in the breast. There were no BIA-ALCL cases found in the included studies for this systematic literature review. However, the literature search excluded certain studies, including those with less than 100 patients per study arm. A search of the excluded articles was conducted to see if there were any articles that may have discussed BIA-ALCL. Among the excluded articles, one study evaluated BIA-ALCL patients at a single institution in a prospective manner to report patient presentation, clinical course, treatment, and outcomes. The details regarding the tissue expander use were not fully provided in the article.

An additional literature search was conducted to determine if there were any publications described in cases of ALCL with medical devices other than breast implants. FDA presented results from a prior literature search on this topic at the 2019 advisory committee meeting. The results at that time showed that ALCL has been associated with devices other than breast implants in the literature including metal implants, polytetrafluoroethylene, polymer vascular grafts, gluteal implants, and lap band. In our updated search, there were two case report studies that described ALCL attributed to nonbreast implants, including a metal femoral rod and fixation and gluteal implant. The quality and quantity of the overall evidence presented in this study is low due to two non-US case reports. However, the report included additional evidence of non-breast implant related ALCL which suggests the issue may warrant ongoing surveillance.

The next three slides provide background information for medical device reports or MDRs. The MDR system provides FDA with information on medical device performance from patients, healthcare professionals, consumers, and mandatory reporters including manufacturers, importers, and device user facilities. The FDA receives MDRs of suspected device associated deaths, serious injuries, and surgeon malfunctions. The FDA uses MDRs to monitor device performance, detect potential device related safety issues, and contribute to benefit risk assessments of these products. MDRs can be used effectively to establish a qualitative snapshot of adverse events for a specific device or device type and detect actual or potential device problems used in a real-world setting or environment including rare, serious, or unexpected adverse events, adverse events that occur during long-term device use, adverse events associated with vulnerable populations, off label use, and use error.

Although MDRs are a valuable source of information, this passive surveillance system

has limitations, including the submission of incomplete and accurate, untimely, unverified, duplicated, or biased data. In addition, the incidents or prevalence of an event cannot be determined from this reporting system alone due to potential underreporting of events and lack of information about the frequency of device use. Finally, the existence of an adverse event report does not definitely establish a causal link between the device and the reported event. Because of these limitations, MDRs comprise only one of FDA's tools for assessing device performance. As such, MDR numbers and data should be taken in the context of the other available scientific information.

To further contribute to benefit risk assessment of tissue expanders, the agency reviewed individual MDRs to identify adverse events related to the use of tissue expanders product code LCJ entered through April 1, 2022. The search resulted in the identification of 3,068 unique MDRs. Of the 3,068 MDRs there were 2,544 serious injury MDRs, 509 malfunctions, five death MDRs, and an additional 10 MDRs that had a blank or other listed as the event type. Of the 3,068 MDR’s included in the analyses, 3,052 report use in the breast and 16 report use in anatomical locations other than the breast. There were no MDRs on accessories associated with tissue expanders. Of the five MDRs that reported a death, two MDRs were for the same patient resulting in four reported deaths. Of the four reported deaths, only one report provided an event narrative, which stated partial necrosis of flap, wound infection, distant metastasis, tissue expander removal, and death. Another report provided the patient's medical history, which includes cardiovascular disease, hypothyroidism, obesity, post operative atelectasis, and productive cough. The remaining two MDRs that reported death provided no additional information.

Additionally, there were 5,573 serious injury MDRs for the product code LCJ that were reviewed through the alternative summary reporting, or ASR program from June 9, 2000 to December 5, 2018. The adverse events reported through the ASR program were similar to the adverse events reported through the MAUDE database. The ASR program enabled manufacturers of certain device types to submit quarterly summary reports of specific well known and well characterized events in lieu of individual reports of each such event. The adverse events reported through the ASR system for tissue expanders were similar to the adverse events reported through the MAUDE database.

The analysis of MDRs associated with tissue expanders that will be discussed in the next few slides includes all events received by FDA through the standard individual MDR reporting mechanism. Of the 3,052 MDRs related to use in the breast, there were 2,531 serious injury reports as shown in the table on this slide. Notably, there were reports of serious injuries for BII and BIA-ALCL. Of the 2,531 serious injury MDRs, 30 report systemic symptoms of the BII. These reports included a description of symptoms including fatigue, brain frog, chronic pain, rashes, itching, and others. Many of the reports reported that symptoms improved or resolved when the tissue expanders were explanted. There were eight MDRs that reported a BIA-ALCL diagnosis after the use of a tissue expander for the breast. Of these eight reports, five MDRs described the use of a textured tissue expander followed by a permanent breast implant. One MDR describes the use of a textured tissue expander with no additional information on the history of other device planted. One MDR describes the use of a breast implant with no additional information on the history of other devices implanted and one MDR describes the use of textured expanders followed by smooth implants.

Given tissue expanders intended for use in the breast are intended to be temporary devices that are often replaced with permanent implants, it is unclear whether temporary exposure to tissue expanders may contribute to long-term safety risks, such as BIA-ALCL and BII. Of the 3,052 for the breast reports, there were 506 malfunctions to report. Note, as the individual submitting the MDR chooses the event type, there may be similar adverse events identified under the serious injury and malfunctions. The top malfunctions reported for tissue expanders included deflated, rupture, or leak, defective device, and foreign body on device. Of the 3,068 MDRs included in the analysis, 16 MDRs reported adverse events with the tissue expander used in locations other than the breast. Of these 16 MDRs, there were 13 reports of serious injury and three reports of malfunctions. Of these 16 MDRs, deflation was reported in 12 of the MDRs, infection was reported in three, and one MDR did not report the type of adverse event. None of these 16 MDRs for tissue expanders used in an anatomical locations other than the breast reported systemic symptoms or any type of lymphoma.

Overall, the MDR analysis shows that there are complications associated with the use of tissue expanders for all indications. The analysis shows that there are specific complications associated with the use of tissue expanders in the breast that may not be found when tissue expanders are used in other anatomical regions. In particular, the MDR analysis shows that there are several reports of BIA-ALCL and BII when tissue expanders are used in the breast.

The medical device recall database contains medical device recalls classified since November 2002. Since January 2017, it may also include correction or removal actions initiated by a firm prior to review by the FDA. The status is updated if the FDA identifies the violation and classifies the action as a recall and again when the recall is terminated. FDA recall

classification may occur after the firm recalling the medical device product conducts and communicates with its customers about the recall. Therefore, the recall information posting date or create date identified on the database indicates the date FDA classified the recall. It does not necessarily mean that the recall is new.

Recalls are classified into a numerical designation one, two, or three, by the FDA to indicate the relative degree of health hazard presented by the product being recalled. A Class I recall is a situation in which there is a reasonable probability that the use of or exposure to a violative product will cause serious adverse health consequences or death. A Class II recall is a situation in which use of or exposure to a violative product may cause temporary or medically reversible adverse health consequences or when the probability of serious adverse health consequences is remote. A Class III recall is a situation in which use of or exposure to a violative product is not likely to cause adverse health consequences.

A search of recalls for tissue expanders and accessories found 10 recalls under product code LCJ. To protect individuals from increased risk of BIA-ALCL associated with Allergan BIOCELL textured breast implants. The FDA requested that Allergan recall its BIOCELL textured breast implants and textured tissue expanders July 24, 2019. Allergan agreed and removed these products from the global market. There were four Class I recalls initiated for this issue. Two Class II recalls were initiated due to certain tissue expanders that may be packed in boxes labeled for another model. Two close II recalls were initiated due to certain tissue expanders that may be packaged in boxes labeled for the wrong size. Two Class II recalls were initiated due to certain tissue expanders that were shipped beyond the product shelf life. Aside from the Allergan BIOCELL recall, the other identified recalls are related to manufacturing

errors and do not suggest additional risks associated with the use of tissue expanders.

To determine the appropriate classification for tissue expanders and accessories, we have identified the risk associated with these devices. To identify the risk of these devices, we reviewed MDRs recall information and the literature analysis as previously discussed and the information available to FDA regarding cleared devices. Here are the five risk categories we identified for all tissue expanders regardless of anatomical location. Skin trauma, device malposition or over inflation with saline may lead to skin trauma such as necrosis, thinning, sloughing, and extrusion. Device malfunction or device failure leading to reoperation. Device malfunction, such as rupture leakage or over inflation or failure to inflate may require reoperation or explantation. Additional risks associated with reoperation include anesthesia risk, surgical time operation, patient dissatisfaction, infection, delay in treatment, scarring, and psychological burden. Infection. Inadequate device sterilization or packaging integrity may lead to infection that may lead to additional surgical procedures. Adverse tissue reaction. Device material may elicit adverse tissue reactions, such as allergic reaction, toxicity, and foreign body response. Pain or discomfort. This can result from device usage.

Here are three additional risk categories to identify for tissue expanders when used in breast. Delay in adjunctive treatment or therapies. The potential to delay chemotherapy or other adjunctive cancer treatment or therapies to resolve any potential complications from the tissue expander use, such as infection. Breast implant illness has been reported following the implantation or presence of tissue expander in the breast. Breast implant associated anaplastic large cell lymphoma. BIA-ALCL redeveloped from the implantation or presence of tissue expander in the breast. Additional details on BII and BIA-ALCL are provided on the next slides.

Some women have reported a variety of systemic symptoms following reconstruction or augmentation with breast implants with or without prior implantation of tissue expanders. The term breast implant illness, or BII, has been used to describe the symptoms, which include but are not limited to, fatigue, problems with memory or concentration, brain fog, joint and muscle pain, hair loss, weight changes, and anxiety or depression. The BII was discussed at the 2019 panel meeting. The BII discussion focused on the constellation of symptoms reported by patients and the lack of defined diagnostic criteria for BII. The panel indicated that many of the symptoms reported have other causes and stress the importance of an appropriate control group to investigate how the numbers reported in breast implant patients compare to the incidents in the general population. The panel also noted that there may be multiple factors which could affect these symptoms, including genetic predisposition in patient and family history. Research continues to be performed to better understand any potential association with breast implant and tissue expanders. Currently, however, BII is not recognized as a formal medical diagnosis and there are no specific tests or recognized criteria to define or characterize it.

In 2011, the FDA identified a possible association between breast implants and the development of anaplastic large cell lymphoma, ALCL. In 2016, the World Health Organization designated breast implant associated anaplastic large cell lymphoma as a T-cell lymphoma that can develop following breast implants. Many tissue expanders are intended for breast reconstruction after mastectomy or trauma. These tissue expanders are commonly used in two stage breast reconstructions where an initial temporary implantation of a tissue expander is later replaced with a breast implant following a period of gradual inflation. The figure on the right shows how a BIA-ALCL is found in the breast. Currently, the risk of BIA-ALCL is largely associated with breast implants and there is limited information to date on whether temporary

exposure to tissue expanders may contribute to that risk.

As tissue expanders and breast implants often have nearly identical constructions as to shell materials, shape, size, and surface texture, tissue expanders may elicit similar immune responses when implanted. Given tissue expanders intended for use in the breast are intended to be temporary devices that are often replaced with permanent implants, it is unclear whether temporary exposure to tissue expanders may contribute to long-term safety risks, including BIA-ALCL or BII. Because the average time to implantation to BIA-ALCL diagnosis is 8-10 years and tissue expanders are not intended for implantation beyond six months, the inherent timeframe of BIA-ALCL pathogenesis may preclude case reports of tissue expanders present at the time of BIA-ALCL diagnosis. Plus direct correlation between tissue expanders and BIA-ALCL diagnosis may be difficult to establish.

To gather additional information about ALCL in women with breast implants, FDA established the registry in collaboration with the American Society of Surgeons referred to as the PROFILE registry. PROFILE standing for patient outcomes for breast implants at anaplastic large cell lymphoma, etiology, and epidemiology. The etiology and pathogenesis of BIA-ALCL remain poorly understood. Potential impetuses for BIA-ALCL, as postulated in the literature, based on limited scientific data includes implant surface texture, patient's genetic predisposition, and the presence of bacterial endotoxins on the implant surface. Additional research is needed on devices that are intended to be implanted to the breast to assess for any possible relation to BIA-ALCL.

Moving to risks associated with accessories. Here are the five risk categories we identify for tissue expander accessories. Skin trauma. Needle injection may lead to minor bruising,

bleeding, or other injury to tissue. Inaccurate reading from port detector may lead to bleeding if injection is made at wrong location. Device malfunction leading to increased operative time. Inaccurate reading from port detector may lead to rupture or leakage of tissue expander or damage or bleeding to surrounding blood vessels or tissues if injection was made at wrong location. Needle misalignment may lead to rupture leakage of tissue expander if needle is inserted at incorrect angle. These examples may lead to increased operative time and additional risks, such as increased anesthesia. Infection. Inadequate device sterilization or packaging integrity may lead to infection that may lead to additional surgical procedures. Adverse tissue reaction. Device materials may elicit adverse tissue reactions, such as allergic reaction, toxicity, and foreign body response. Pain or discomfort. This can result from device accessory usage. Now, we will move on to the recommended mitigations for the risk identified for tissue expanders used in the breast used in other anatomical locations and tissue expander accessories.

First, we'll discuss tissue expanders intended for use in the breast. Given tissue expanders intended for use in the breast are intended to be temporary devices that are often replaced with permanent implants. It is unclear whether temporary exposure to tissue expanders may contribute to long-term safety risks. For example, BIA-ALCL or BII. FDA believes that the risk of BIA-ALCL and BII potentially occurring with tissue expanders intended for use in the breast may not be mitigated by special controls. Ability to have more stringent post-market oversight typically associated with Class III devices, such as annual reports and reports of manufacturing changes, can offer a means to monitor the devices and offer reasonable assurance of safety. FDA proposes that tissue expanders intended for use in the breast meet the statutory definition of a Class III device because insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of their safety and effectiveness. Additionally, tissue

expanders intended for use in the breast present a potential unreasonable risk of illness or injury based on limited clinical information that has been obtained.

For tissue expanders intended for use in other parts of the body, or nonbreast use, FDA proposes that they meet the statutory definition of Class II device. We believe general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness and sufficient information exists to establish special controls to adequately mitigate the risk to health and provide reasonable assurance of device safety and effectiveness for this device type. Here is a table with the identified risks as listed on the previous slide and proposed mitigation measures, which we believe can be addressed through special controls.

For tissue expanders intended for use in other parts of the body, or nonbreast use. To mitigate the risk of skin trauma, we recommend performance testing and labeling. To mitigate the risk of device malfunction or device failure leading to reoperation, we recommend performance testing and labeling. To mitigate the risk of infection, we recommend sterilization, testing, validation, and information. Shelf life validation, and labeling. To mitigate the risk of adverse tissue reaction, we recommend biocompatibility, evaluation, and labeling. To mitigate the risk of pain or discomfort, we recommend labeling.

FDA proposes that tissue expanders meet the statutory definition of Class II device. We believe general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness and sufficient information exists to establish special controls to adequately mitigate the risk to health and provide reasonable assurance of device, safety, and effectiveness for tissue expander assessments.

FDA has identified the following mitigations for the risks previously identified for tissue

expander accessories. To mitigate the risk of skin trauma, we recommend performance testing and labeling. To mitigate the risk of device malfunction leading to increased operative time we recommend performance testing and labeling. To mitigate the risk of infection, we recommend sterilization testing and validation information, shelf life validation, and labeling. To mitigate the risk of adverse tissue reaction, we recommend biocompatibility evaluation and labeling. To mitigate the risk of pain or discomfort, we recommend labeling.

Here is our proposed classification regulation for tissue expanders and accessories. Part A of the regulation defines the device as follows. A tissue expander is an inflatable silicone elastomer shell filled with normal physiological saline intended for temporary implantation to develop surgical flaps or additional tissue coverage in surgical applications. Tissue expanders may have a smooth or textured surface and are filled through an injection port. A tissue expander is intended for temporary subcutaneous or sub muscular implantation not to exceed six months. The device includes tissue expanders intended for use in the breast, tissue expanders intended for use in other parts of the body, or nonbreast, and accessories for tissue expanders.

Here is our proposed description of tissue expanders used in the breast. Tissue expanders intended for use in the breast are generally round in shape and have varying fill volume range width range, height range, and projection range. They have multiple suture tabs for an option. They may have multiple suture tabs for an option to suture to surrounding tissues. They are intended for breast reconstruction after mastectomy or other trauma, correction or treatment of an underdeveloped breast, treatment of soft tissue deformities, or a combined chest wall and breast deformities.

Here is our proposed description of tissue expanders used in other parts of the body or

nonbreast. Tissue expanders intended for use in other parts of the body, nonbreast, can have different shapes including rectangular, cylindrical, U shaped, and crescent. They have varying fill volumes and dimensions. Tissue expanders for other parts of the body, or the nonbreast, are intended for soft tissue expansion, such as scar revision and treatment of tissue deformity or injuries and anatomical locations other than the breast.

A proposed description of tissue expander accessories in this is as follows. Accessories common to tissue expanders in the breast and other anatomical areas can include port detectors, fluid dispensing systems, needle infusion sets, external fill ports, and syringe assists. Furthermore, we are proposing these devices be classified as follows. One. Class III premarket approval when intended for use in the breast. Two. Class II special controls when intended for use in other parts of the body or nonbreast. Three. Class II special controls for tissue expanders and accessories.

Based on the identified risk and recommended mitigation measures previously identified for tissue expanders intended for use in other parts of the body or nonbreast, FDA believes that the following special controls will provide reasonable assurance of safety and effectiveness for tissue expanders intended for use in other parts of the body or nonbreast. One. The patient contacting components of the device must be demonstrated to be biocompatible. Two. Performance data must demonstrate the sterility of patient contacting components of the device. Three. Nonclinical performance testing must demonstrate that the device performs as is intended under anticipated conditions of use. The following performance characteristics must be tested. One. Mechanical assessment of the shell, including tensile strength, percent elongation, tensile set, and joint testing. Two. Shell surface characterization, including manufacturing methods, surface roughness, or texturing. Three. Injection site testing to show that tissue expander can be accurately assessed. Four. Valve competency testing if applicable to demonstrate that valve

integrity is maintained at in vivo loads. Five. Self sealing patch testing if applicable to demonstrate a punctured patch can self seal and maintain that self seal for the duration of use. Number four. Performance data must support the shelf life of the device for continued sterility, package integrity, and functionality over the requested shelf life. Number five. Labeling must include: One. Information on how the device operates in the typical course of treatment. Two. Warning related to use beyond tissue tolerances, which may result in tissue damage. Three. The risks and benefits associated with the use of the device. Four. Post operative care instructions. Five. Alternative treatments. And six. Shelf life.

Based on the identified risks and recommended mitigation measures previously identified for tissue expander accessories, FDA believes that the following special controls would provide reasonable assurance of safety and effectiveness for tissue expander accessories. Number one. The patient contacting components of the device must be demonstrated to be biocompatible. Number two. Performance data must demonstrate the sterility of patient contacting components of the device. Number three. Nonclinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. Number four. Performance data must support the shelf life of the device for continued sterility, package integrity, and functionality over the requested shelf life. And number five. Labeling must include one, information of how the device accessory operates. Two, the risks and benefits associated with the use of the device accessory. And three, shelf life. This concludes our presentation. Thank you for your time and attention.

Dr. Harris: Thank you. At this time, I would like to take any questions from the panel members clarifying any specific element of that presentation. After those clarifying questions

have been addressed, we'll take a short 10 minute break after which we'll return and hear the specific FDA panel questions and begin our deliberations as a committee. So, if there are any clarifying questions, any points you would like to have addressed or clarified regarding the presentation we just heard, let's have that now. Dr. Armstrong.

Dr. Armstrong: Yes. Thank you. This is Deb Armstrong. I had two questions about the MDR reporting. There were 3,068 identified. Can you clarify over what period of time that was? And then I have a second question.

Dr. Dean: I believe that was from the beginning of our collection of such reports up until this spring when the panel summary was put together, but that information is in your summary packet.

Dr. Armstrong: Yeah. I'm sorry. I looked for it. I didn't actually find anything. So you would say is that's -- is that -- really -- is that from the last maybe five years?

Dr. Dean: No. No. No. Much longer. From the beginning of our reporting, I believe.

Dr. Armstrong: So, the late 90s?

Dr. Dean: I can check with the team and clarify that.

Dr. Armstrong: I remember your timeline thinking [indiscernible]. So, is there a true denominator known for this, which is not just the number of -- so, if you look at the BIA-ALCL, it's about .25% is 8 out of a little over 3, 000, so about .25% of the MDRs reported. But I think potentially and equally important question is what is that out of all of the tissue expanders used during that period of time? Because this is certainly a fraction of the reports, but it's obviously going to be a smaller fraction of those used and do we have a ballpark of what

numbers were used during that same period of time?

Dr. Dean: Sorry I didn't introduce myself earlier. Well, I introduced myself. I didn't say earlier this is Heather Dean speaking. So, unfortunately, one of the limitations of the MDR system is that there is no denominator. This is a passive reporting system. We only receive only the device event reports and we do not know how many actually are out there. And I did get clarification on the beginning time for the event reporting. That is since 1986.

Dr. Armstrong: Okay. I mean, there probably should be just some public data. Not FDA data, but how many tissue expanders were used during that period of time and what percentage had an MDR. That would just I think be useful information to get a true sense of what the rate of the malignancy is.

Dr. Dean: Agreed. Unfortunately, our system is limited and we don't have that denominator information.

Dr. Harris: Next question from Dr. Li.

Dr. Li: Yes. This is Stephen Li. A very similar question. I understand the FDA may not know the total number of tissue expanders themselves. But certainly there must be marketing data or sales data or some kind of business database that gives you the size of the market to give you a total number of tissue expanders sold. Certainly somebody knows the total market size. And the second question is in the area I work more in orthopedics, our experience on the MDR is a very small percentage of actual failures actually get reported to the MDR. In some cases the clinical failure is upwards of 10 or 12%, but the MDR reporting was less than 1%. So, does the FDA have any feeling for what percentage of actual failures get reported to the MDR?

Dr. Dean: Unfortunately, no. As was mentioned and as you brought up, the MDR

data it is limited in several ways. Not knowing that denominator and also the underreporting. It can be useful in monitoring device performance or spotting trends or detecting unexpected events that would occur only once the device is in the real-world setting. It's also useful in detecting rare and/or serious adverse events, but there are a number of limitations.

Dr. Li: So, just as a quick follow-up. Are any of the speakers from the ASPS, would any of them have any idea what the total market size is with this? If they are still around?

Dr. Harris: Anyone?

Dr. Matarasso: It's Alan. Yeah. It's Alan Matarasso. I'm a plastic surgeon in New York. I think both of these two questions are critical. Can I ask you, are you able to pull up the slide with the MDR data with the complications and numbers? And going to try and give you some sense of what a numerator might look like because I don't think we can really interpret the data without a numerator. This could represent 0.1% or 50%. So, that's going to be important. Can you go back to that slide?

Dr. Dean: I want to make sure that we don't get too into the weeds here because, as has been mentioned, this is very limited information. We really can't say much about even if we knew how many devices were in the market, the incidence or prevalence of an event really can't be determined from this reporting system alone due to the underreporting that Dr. Li mentioned. Also, just lack of information about the frequency of device use. So, I want to make sure that we stay focused on clarifications from the presentation and move on to the questions.

Dr. Matarasso: The presentation was excellent. Just the question I have because I want to shed some light onto these earlier two questions. That was for how long a time period of time approximately? And what data? I don't want to get -- yeah.

Dr. Dean: Approximately 1986 until this past spring.

Dr. Matarasso: That's 36 years. And I'm just going to give them panelists a sense of what we're looking at. 36 years. There's over 100,000 breast reconstructions done in this country a year and conservatively 65-80% of those are done with tissue expander. I'm sorry, with implants. And many of the implants required a tissue expander before implantation. So, if we just look at that number on a very, very conservative basis, you have 65-80% of the breast cancer reconstructions are with implants as opposed to taking your own body tissue. And I can't tell you exactly what percentage those require tissue expanders, but a high percent do. So, you are looking at at least I would think 50,000 a year times 36 years as a denominator if that sheds some light. And then more directly to answer the question, obviously the manufacturers have the data about how much they sell. Unfortunately, there's been a lot of consolidation on the manufacturer's part and sales, so the companies that existed in 1986, many of them don't exist now. But hopefully that gives some light onto the degree of use.

Dr. Harris: Thank you. Next question. Dr. Ballman.

Dr. Ballman: Yeah. Hi. This is Karla Ballman. And I'm just trying to just figure out sort of the rationale between why Class III for the breast expanders and why Class II for the nonbreast. My feeling is that the vast majority of expanders are done in breast, so that would just have higher numbers and more likelihood to see the rare events. Is it just because of the breast related lymphoma and illness that distinguishes the two? Because I'm just having a hard time figuring out why implantation or why use in the breast would have different risks than used elsewhere.

Dr. Harris: I just want to step in one other time. Great question. My interpretation of a

clarifying question would be FDA asking that there be a differential classification for breast expanders versus breast accessories. The content of the response to your question I think we should save for our deliberation. Great question, but I just want to get any clarifications about what they presented. Then we'll talk about the content that they presented.

Dr. Ballman: Okay, so, I will rephrase --

Dr. Harris: Well, hold that. I'll get back to you.

Dr. Ballman: -- according to how Dr. Harris has stated it.

Dr. Harris: Thank you. Dr. Pusic.

Dr. Pusic: I'm totally happy to say if this is not a clarifying question let me know and we'll move on. It's a small point, but a question to FDA in terms of -- it's a small, but I think it's a clinical question about the six-month period for tissue expanders to be in place and where that range came from. And the reason I ask is that it's not the most common scenario, but it's certainly not rare for a patient to have a tissue expander in for medical reasons, medically necessary reasons for longer than six months. The example would be is you have a tissue expander placed at the time of a mastectomy. She might require post mastectomy chemotherapy followed by radiation, and then we can't safely remove the device for perhaps six months after that. So just -- if that's a clarification, but perhaps something to discuss later.

Dr. Harris: I'm going to call on Dr. Ashar. I'm sorry.

Dr. Dean: I was going to say we agree, but I think our point is any of these devices are indicated for use up to six months. How they are used in practice can differ, but many are indicated for up to six months.

Dr. Ashar: Yes. I will lower my hand. Thank you so much. I think this is a great line of questioning. Just I know we are going to discuss Dr. Ballman's question a little bit further during the session. However, just to address part of it now, the scope of this discussion is tissue expanders. The team performed an analysis related to adverse events. We looked at the benefits and risks and these are unclassified devices and are proposing for your consideration whether the risks can be mitigated with the risk mitigation information that Dr. Tajanay Ki presented or not. So, that is the focus of this conversation. The MDR information, the information regarding rates of use and use of the PROFILE registry, as well as the national breast implant registry to collect long-term information. That's all used together. So, I would advise the panel to not focus on any one bit of evidence upon which everything else is hinged and to look at the body of information that you have before you to see if that risk mitigation table that Tajanay Ki presented makes sense or if you have other thoughts or suggestions pertaining to the risks associated with these devices and the mitigations that we have proposed for your discussion. Thank you so much.

Dr. Harris: Dr. Armstrong.

Dr. Armstrong: Yes. This is Deb Armstrong. I had kind of a separate question about the literature search because I think we all appreciate that there are healthcare systems in other countries where essentially all data on all patients is centralized and known so that you could connect the incidence of ALCL with whether or not somebody had a breast implant. And looking through the list of -- I don't know what South Korean healthcare system is or Italy, but whether there were any of those where potentially could be weighted more heavily because they are healthcare systems where you will be able to know without anybody having to report it whether there's somebody who had a breast implant or tissue expander and somebody who had

ALCL. Which would to me would at least be valuable information in terms of understanding the actual risk. And I don't know if -- I mean, I can look through that list, but I honestly don't know if any of those or healthcare systems that would be expected.

Dr. Dean: I don't know, but we can get back to you with additional details after the questions have been played and that discussion begins.

Dr. Harris: Great. If there are no other burning clarifying questions, I would like to give us, the committee, a 10 minute break. Actually, make it nine minutes so we can come back at what would be 11:20 a.m. Eastern Standard Time. So, we'll see you in nine minutes. Thank you very much.

Dr. Harris: Well, welcome back to all the panelists and public participants. I would like to begin by announcing we have the pleasure of being joined by yet another esteemed panel member. Miss Sandra Agazie. We are going to ask that she introduce herself and tell us more about her appointment and expertise.

Sandra Agazie: Good morning, everyone. Thank you for having me. My name is Sandra Agazie, Chief Executive Officer of Sanzie Healthcare Services and my profession is in nursing and one of the panelists as well. Thank you.

Dr. Harris: Thank you. We are now going to move, as you know, to discussing the panel questions that the FDA is posing for us. I would like to remind everyone to remember to identify yourself every time you speak and make sure your microphone is unmuted. If we can please have FDA present the first question for our panel to deliberate.

Ms. Ki: We have the following questions for the panel. We are looking for your thoughts and recommendations on the appropriate regulatory classification for these devices.

Question one. According to 21 CFR 860.7(d)(1), there is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from the use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use outweigh any probable risks. The valid scientific evidence used to determine the safety of the device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use. In addition, according to 21 CFR 860.7(e)(1), there is reasonable assurance that a device is effective when it can be determined, based on the part valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses, and conditions of use with a company by adequate directions for use and warnings against unsafe use will provide clinically significant results. Please address the following questions regarding the risks to health posed by tissue expanders intended for use in the breast. FDA has identified the following risk to health for tissue expanders intended for use in the breast based upon literature and our search of adverse events submitted through Medical Device Reports, or MDRs. The risks include skin trauma, device malfunction, or device failure leading to reoperation, infection, adverse tissue reaction, pain or discomfort, delay in adjunctive treatment or therapies, BII and BIA-ALCL. This list may not be exhaustive. Identified risks could result from the reported device related adverse events, including device leakage or rupture, over inflation, and inadequate sterilization. Given tissue expanders are intended for use in the breast are intended to be temporary devices that are often replaced with permanent implants, it is unclear whether temporary exposure to tissue expanders may contribute to long-term safety risks. For example, BIA-ALCL and BII. The risk of BIA-ALCL and BII potentially incurring tissue expanders used in the breast present a potential unreasonable risk of illness or injury based

on limited clinical information that has been obtained. Please comment on whether you agree with inclusion of all these risks and the overall risk assessment of tissue expanders intended for use in the breast. In addition, please comment on whether you believe that any additional risks should be included in the overall risk assessment of tissue expanders intended for use in the breast. Given the available information, please comment on whether there is reasonable assurance of safety for tissue expanders intended for use in the breast. While the literature information focused on safety, tissue expanders may be effective for use in breast reconstruction and may offer benefits, including delayed reconstruction and flexibility with oncological treatments. Tissue expanders have also been cleared for correction or treatment of the underdeveloped breast or treatment of soft tissue deformities or a combined chest wall and breast deformities. Please comment on whether there was a reasonable assurance of effectiveness for tissue expanders intended for use in the breast.

Dr. Harris: Okay. So, our first question as a panel is do we feel that all of the risks that were just listed are appropriate and subpart of that question is are there any additional risks that should be added or any of those risks that should be removed? I'll open it up for comments. Dr. Bryant?

Dr. Bryant: Lamont Bryant. Question or specific with the question. These risks are associated with a procedure or are they supposed to be associated with the actual product itself? Because some of those risks I can argue could be procedure related. Just want to make sure we are having the right conversation.

Dr. Harris: I will have FDA comment, but my interpretation is these are risks associated with the device. Not necessarily the surgical procedure. Anyone from FDA like to

respond to that question? Dr. Dean?

Dr. Dean: I believe these are, and David can correct me if I'm wrong, but I believe these are risks associated with the use of the device, which would include the procedure.

Dr. Harris: Dr. Bryant, does that answer your question?

Dr. Bryant: Sort of, kind of. I think the difference between the device itself and the actual practice of medicine, the procedure so I'm trying to tease out both. It actually doesn't. So I'm really trying to get my mind around the device itself and complications associated with the device, compatibility and things of that nature, versus position by physician, technique or procedural patient reaction, if you will. Procedural reaction.

Dr. Dean: We are looking at the risks that are associated with the device and device use for the indicated uses. So risks that are associated with off label use, use beyond the time indicated. That's not what we were looking at here. We are looking at those risks associated with indicated device and device use.

Dr. Bryant: That answered my question, thank you.

Dr. Harris: Thank you. Dr. Seidman.

Dr. Seidman: So, two comments. One a small quick one and the other is a little bit deeper. I was actually surprised that in no reporting had rib fractures ever been reported. Something I've seen in my own practice is that patients who have had particularly tight expanders have had anterolateral rib fractures ipsilateral to the expander. I just want to throw that out there. The second deeper issue is related to how BII and BIA-ALCL are kind of mentioned in the same breath. It almost validates what the FDA admits is an uncertain diagnosis of the latter of

breast implant illness. Clearly ALCL is a pathological diagnosis. I suspect as a medical oncologist that I am responsible for a lot of the breast implant illness, which can be attributed to chemotherapy and post chemotherapy fatigue and cognitive dysfunction, aromatase inhibitors, -- etc. So I just want to throw that out for consideration that whatever language is ultimately in a label may not put BII and ALCL on the same level playing field.

Dr. Harris: Thank you. Dr. Hunt.

Dr. Hunt: Yes. Hi. This is Kelly Hunt. I had a question about having BIA-ALCL associated with all expanders since I think it's really the textured devices that this is associated with. And then also, in terms of Dr. Bryant's question, I think it is challenging in many ways to separate the procedure from the device and the procedure has a lot of associated things related to it. So, I think that perhaps the wording could be changed somewhat to reflect those different aspects related to the real world practice of surgery. Thank you.

Dr. Harris: Dr. Armstrong.

Dr. Armstrong: Thanks. This is Deb Armstrong. I guess kind of along with Dr. Seidman, there have been at least a few instances where patients with tissue expanders have had issues at the surgical site that would optimally be evaluated with an MRI and are not able to get MRI. I think this is actually because I don’t think it's the expander and maybe the surgeons can help me with this, but maybe it's the magnetic port localizer that is the problem, but I don't know, and I don't know if there would be a way to track this, but to me that's been probably the biggest issue that I've come across as a potential issue in people with tissue expanders, and I don't know how one would track that, but I would look at that as a potential problem that if can be should be tracked.

Dr. Harris: So, is your thought that perhaps there should be an added risk for patients to understand that having this device in place could prevent them from undergoing certain diagnostics?

Dr. Armstrong: Yes and I think the patients I've had with that were really upset that the expander really precluded them from getting the evaluation that was felt to be most appropriate. Usually these are people with papular granuloma abnormalities that are concerning for a local recurrence. I would absolutely say that should be a part of it.

Dr. Harris: Ok, thank you. Dr. Hunt, your hand is still up. I don't know if you want to put it down or if you have a new comment.

Dr. Hunt: No. I will put it down.

Dr. Harris: So, any other thoughts about that particular list of risk? What I've heard so far is that we may or there may be reason to add a risk regarding limitations of diagnostic imaging as a result of having the implant in place? And then there was some discussion around perhaps trying to tease apart risk associated with the device versus the use, the implantation procedure. I don't know if that was exactly Dr. Bryant's intent.

Dr. Bryant: Lamont Bryant. Dr. Harris, that was it. If we can look at the list as we continue to deliver it. I know we are at the end of it, but just to better articulate specifically a couple of concerns specifically around procedures versus product.

Dr. Harris: Okay. Dr. DeLong.

Dr. DeLong: Yeah, I just, I wanted to chime in on that topic. Not just specifically procedure, but the reconstructive process as a whole, represents particularly as we look at delay

in cancer treatment. I think that's one of the three kind of key elements that would decide whether this should be Class II or Class III because it's one of the ones that are not listed can be mitigated by special controls, but anytime we do reconstruction on a patient if we do a flap, if there is a mistake a skin flap occurs it leaves the patient in a position where we may have to delay radiation. It's not even the specific procedure putting in the expander, but it's the patient going through the reconstruction process and immediate reconstruction process at all. Again, I'm sort of echoing LaMont's point of how do we decide whether that's a device risk versus just a practice of medicine reconstructive risk.

Dr. Harris: Any other thoughts from the panel on either that comment or additional comments? Dr. Armstrong.

Dr. Armstrong: Yeah. I would say, and Dr. Seidman can maybe chime in here. The six-month limitation is a little bit surprising to me. I actually didn't realize that because with some of the treatment regimens that we use today, just the chemotherapy portion, can go on for maybe at least six months. And even people who are getting neoadjuvant therapy, so they haven’t had breast surgery, a HER2-positive patient will be recommended to have 14 cycles of chemotherapy therapy after that. I was kind of surprised at that six-month because a lot of patients will be getting systemic therapy for six months or close to it and some of them for even longer. Obviously, you want these to be removed after radiation and frankly after some healing from radiation. I think with today's chemotherapy regimen and radiation planning, I don't know if that six months is rational.

Dr. Harris: So, on that one point, I'd like to have the FDA comment. It's my understanding, if I understand you correctly, that is the current indication for use or labeling of

the device. Is that correct, Dr. Dean?

Dr. Dean: That's my understanding is that many of these devices are indicated for use up to six months. However, we welcome your input on any types of risks, including how these devices are actually used in practice and we will incorporate that into our thoughts on this classification.

Dr. Harris: Dr. Pusic.

Dr. Pusic: Andrea Pusic. Totally agree with what Dr. Armstrong has just said, but my comment was more in support of Dr. Bryant's comments and really, just as a clinician, the example that comes to my mind is a patient might say have a hematoma related to a blood vessel just opening up after surgery and we have to take the patient back in that case. The scenario where it's related to the device, and actually, we have been seeing this to some extent. I have seen this and colleagues have; The new tissues that have tabs eroding into an internal mammary vessel and presenting as a late hematoma, meaning a blood vessel with a start bleeding maybe a couple weeks out, which is very uncommon and device related. I think it is very important to figure out the nuance of this question. What are standard surgical risks related to the surgery and then what is the increased risk of some of these complications specifically related to the device?

Dr. Harris: So, that would actually be then two comments. One is delayed hematoma and/or I guess surgical site occurrence and then there was another one about associated rib fractures. Two issues that I don't seem to be well contained within a list of potential risk. Dr. Seidman.

Andrew Seidman: Follow up, Dr. Armstrong alluded to the difficulties in obtaining necessary MRI imaging, I think focused on finding new breast disease because of some metal

component of the expander or valve. In my own practice, I've encountered a number of occasions where it was actually central nervous system concerns. The patient with a triple negative for HER2-positive breast cancer who developed a headache neurological symptom and couldn't have a medically indicated brain MRI possibly on occasion with a low Tesla machine, which is not readily available widely. So, that's another potential limitation in terms of diagnostic imaging while the tissue expander is in place.

Dr. Harris: Any other questions or comments regarding the list of risk in their mitigations that were presented in question one and 1B? Dr. Dean, it seems as though the committee agrees that list with the content of that list, has raised some additional concerns that you've heard relating to other types of injury that may be associated with the placement of these discs, these devices. Perhaps some way to tease apart what are common surgical risks versus unique risks that can present after placement of the device, such as erosion into a blood vessel with hematoma or surgical site occurrences, and/or perhaps even the development of rib fractures with over hyper inflammation of the device. Is that adequate for you, Dr. Dean?

Dr. Dean: That is. Thank you for your input.

Dr. Harris: Great. Now we can move onto the next question if FDA will read that for the panel.

Ms. Ki: Section 513 of the food, drug, and cosmetic act states the device should be Class III if: insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of its safety and effectiveness, And the device is purported or represented to be for use in or human life, Or for a use, which is of substantial importance in preventing impairment of human health or if the device presents a potential

unreasonable risk of illness or injury. The device should be Class II if general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness and there is sufficient information to establish special controls to provide such assurance. A device should be Class I if general controls are sufficient to provide reasonable assurance of the safety and effectiveness or insufficient information exists to determine that general controls are sufficient to provide reasonable assurance of the safety and effectiveness or establish special controls to provide such assurance. But it's not purported or represented to be a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health and does not present a potential unreasonable risk of illness or injury.

Please discuss the following questions. A, FDA believes that tissue expander intended for use in the breast present an unreasonable risk of illness or injury. Based on the literature search conducted and the evidence obtained from review of MDRs, several risks to health have been identified, including BII and BIA-ALCL. Given that tissue expanders for use in the breast are intended to be temporary devices that are often replaced with permanent implants, it is unclear whether temporary exposure to tissue expanders may contribute to long-term safety risks for example, BII or BIA-ALCL. Although there was very limited information from our literature search on BII and BIA-ALCL with tissue expander use in the breast, MDR reports of BII and BIA-ALCL after tissue expander use in the breast have reported or described these risks with tissue expander use. Additionally, while tissue extenders may be effective for use in breast reconstruction, there are alternatives to breast reconstruction. For example, no reconstruction, external prosthesis, autologous tissue reconstruction, or not using a tissue expander. Therefore, the risk of injury is unreasonable given the lack of probable benefit. Do you agree with this assessment? If not, please explain why. Please discuss the following questions. B. FDA believes

that insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness of tissue expanders intended for use in the breast. Given the limited available information of the long-term effects of these devices when used in the breast, FDA does not believe that special controls can be established to mitigate the known risk to health associate with these devices. Do you agree with this assessment? If you disagree with this assessment, please identify the valid scientific evidence available in support of a reasonable assurance of safety and effectiveness of tissue expanders intended for use in the breast. In addition, please identify the special controls that could be established that you believe would be sufficient to mitigate the risks of health and provide a reasonable assurance of safety and effectiveness of tissue expanders intended for use in the breast. In accordance with 21 CFR 860.10(a), if you recommend a classification other than Class III for this device, please discuss your reasons for the recommendation.

Dr. Harris: Great. So, now, we are being asked to discuss the risk assessment of the tissue expanders and our evaluation of the FDA's conclusions regarding the recommendation this be a Class III device given insufficient data to identify adequate special controls. So, any comments or questions? Dr. DeLong.

Dr. DeLong: This is Mike DeLong. I guess one question I had is what our workable definition of reasonable is? Particular when thinking about the BIA ALCL risk. Dr. Matarsso did a better calculation in terms of the denominator pre-number of tissue expanders likely placed in the United States earlier and reviewing the data from profiling MDRs I think we had one case in PROFILE where the patient had a tissue expander and no following implant and then there was one case in the MDRs where there was no clear description whether an implant was placed or

not, so we are left with basically two potential cases where we can directly attribute the cancer to the tissue expander and those were most likely the textured bio cell expanders, which are no longer in market. When trying to assess what a reasonable risk is, where are we drawing the line for this?

Dr. Harris: Well, where would you draw the line?

Dr. DeLong: I don't exactly know. You know, from the FDA presentation earlier, it does seem ALCL has been found around other implants in rare cases, so it's worth talking about a risk of one or two known cases without specific device type, then that would open the door for pretty much any of those devices that have had ALCL around it to therefore represent an unreasonable risk of ALCL. It seems like having more of maybe one or two cases might be necessary to call it a reasonable risk over a period of 30 years.

Dr. Harris: Thank you. Dr. Hunt.

Dr. Hunt: Yes. Hi. My question was about how the alternatives for breast reconstruction were listed because the idea that autologous tissue reconstruction as an alternative is really not the case for many, many patients. Either based on body habitus or previous surgeries or other things. I'm not sure that it's reasonable to state that is an alternative option for even, you know, a significant percentage of patients. Thank you.

Dr. Harris: Thank you. Dr. Armstrong?

Dr. Armstrong: This is Deb Armstrong. I would agree with Dr. Hunt. The list of alternatives really would exclude what most patients are getting with their surgery today and I think, you know, they really I think would not be acceptable to many patients. This is the reconstruction there's a lot of facets to it, the sort of road to recovery and healing from having the

diagnosis of breast cancer I think that this is part of it and removing an option for those patients I think is detrimental. So, I did have one other -- I just wanted to clarify. Are we addressing right now just the breast implant? Okay. We'll have a separate question for the others.

Dr. Harris: I just wanted to probe a little further into your comment. So, would you translate that lack of other alternatives as an increased tolerance for risk associated with this particular option or this device?

Dr. Armstrong: Well, I think it gets into what you call risk. Is it life-threatening? No, it's not life-threatening. You can make an argument that no woman with breast cancer needs to have breast conserving therapy or to have reconstruction because that doesn't impact whether they live or die, but these are important issues for women with breast cancer because they are quality-of-life issues. This is not a survivor issue. If that's all we were concerned about, you just do a mastectomy and they wouldn't do breast conserving therapy. You wouldn't do reconstruction. I think the technical criteria of it being, you know, health, risking health, I don't think it meets that criteria, but I think we want to do more than just we want to make our patients as whole as they can be again after cancer diagnosis.

Dr. Harris: Thank you. Dr. Seidman.

Dr. Seidman: Sort of to continue on that kind of theme and turn it upside down a bit. We spent a lot of time focusing on risk, and of course it’s risk-benefit analysis, and relatively less time speaking about benefit. I would have liked to have seen a little bit more in the executive summary and perhaps the presentations on benefit compared to the alternatives, and we’ve heard the alternatives include no implant going directly to implant without expander. And autologous tissue reconstruction probably for me since we are drilling down on the risk-benefit analysis of

the tissue expander. I would be curious about comparative quality-of-life data and outcomes comparing expander to implant sequentially versus direct implant. I don't think I saw a whole lot of that.

Dr. Harris: Thank you. Ms. Fisher.

Ms. Fisher: Yes. Melissa Fisher speaking on behalf of patients as a bilateral breast cancer who has had this procedure. Again, and speaking for the alternatives are I really find them to be quite inferior. Certainly for the prosthesis are not really an option for a lot. Procedures again in terms of body, the type of shape of your body is and prosthesis aren't. I find from the patient perspective really not equivalent at all. If they are treating patient I know they are being more holistic and approach. I know doctors are trying to do a better job of doing that. And psychologically speaking, it's very important from the patient's perspective as how they feel, how they are going to feel after this whole procedure. Having enough of a war trying to battle their cancer so how would they feel about their whole body image for some afterwards is widely important. I think it was not addressed enough about what the alternatives were. As I mentioned previously, taking away some of the options, again, I know the risk reward toward it, but again, I think -- I just don't think it was investigated enough in terms of the risk reward for such a short period of time for the expanders. Again, I know it's six months, I didn't realize it was this long after that, but I don't know if there's enough research to make correlation for the bigger problems that come after. That's my comments.

Dr. Harris: Thank you. I think -- I don't think that there's any debate about the value of the device to patients. I think the question that FDA is wanting our input is how do we evaluate the safety? How do we recommend these devices be regulated from a safety perspective

and ultimately should these be classified as a Class II or Class III device? I don't know if you have any thoughts about that, Ms. Fisher?

Ms. Fisher: I guess is, around about, not articulating well enough as I'm battling between the Class II and Class III I guess is where I come down on is the specifics about whether it does necessarily fall into the Class III. I mean, I'm not voting, but I couldn't quite get to the Class III because of unreasonable risk of illness or injury. I couldn't find myself getting there because of these other issues.

Dr. Harris: Thank you. Dr. Matarasso.

Dr. Matarasso: Thank you. I would echo with the previous speaker had mentioned. I just want to go back to the use of the term unreasonable. My difficulty here is, as Dr. Pusic pointed out, device specific versus surgery. And then, you know, notwithstanding the fact that many AE's are not reported to MAUDE. The denominator here is enormous. And so, I'm not sure that with the numerator we have that it relegates us into unreasonable. Finally, an earlier speaker mentioned about alternatives. I could wear the panel down with why people don't prefer the alternatives. There much longer, much riskier, much more expensive. They are only done by certain centers done by specialized people. I'm having trouble with the use of the term unreasonable. Thank you.

Dr. Harris: Great. Thank you. Dr. Pusic.

Dr. Pusic: Thank you. Again, to add to the comments, I am supportive of the designation of Class III. I would, however, in terms of communication to patients I would appreciate the discussion of quality life and benefits. There was a very robust literature around quality-of-life benefits of breast reconstruction among well-informed women who chose that

procedure, well selected and well-informed patients. I think it's very important to keep that in mind. And then I would just also have the clarification that in the same way of many women are either not candidates for or do not have access to autologous reconstruction, the same applies to direct implant reconstruction. It is a minority of women candidates for direct reconstruction.

Dr. Harris: Thank you. Dr. Hunt.

Dr. Hunt: Yes. Just want to follow up on that information about alternatives. Just as was talked about with respect to autologous tissue reconstruction, direct implant reconstruction is often only appropriate for a minority of patients who have very early-stage disease who don't require any skin re-section- there's really disease related and patient related factors that weigh into the type of reconstruction the patient can undergo, and I would agree with Dr. Pusic that it's a minority of patients who can have direct implant reconstruction. A small percentage who can have autologous reconstruction. Just in terms of alternatives, I think it would give people the wrong impression when you state that that is an alternative broadly as if it really is available to everyone and it's not. There's disease related factors and patient related factors. Thank you.

Dr. Harris: Thank you. Dr. Bryant.

Dr. Bryant: Back to the conversation around reasonable assurance, safety, and effectiveness. I will double-click on what was articulated earlier. With the low numbers. All cases are important and should be focused on. With a low number of confirmed BIA-ALCL, I just don't see how this qualifies as unreasonable, specifically around the safety conversation. I just want to weigh in again on that point.

Dr. Harris: Thank you. Dr. DeLong.

Dr. DeLong: I also want to reiterate the discussion on the alternatives. As Dr. Matarasso

said earlier from her survey data, 50 to 80% or whatever autologous -- not autologous but reconstruction patient standard, it really is the sort of workhorse for reconstruction it's a very important tool we use for most patients. But then I also wanted to explore the types of data that are permissible for a Class II verse's a Class III designation are not permissible, but required. Class II go through special controls, Class III allows the FDA to ask for clinical data, but is currently indicated for only six months, I think a six-month core study or premarket study by the FDA may be incapable of differentiating devices based on risk for BIA-ALCL or BII and that may not result in any type of meaningful data in terms of safety of these products. Additionally, looking in post market space, when the first implants were approved in 2006 with a Class III designation there was the 40,000 person approval study. Again, we didn't really learn anything about BII or BIAL-ALCL from those studies. What we know about BII BIA-ALCL came from terrific work from the patient advocates and work from the professional societies building PROFILE register. And so, if these were min Class III, it's not clear to me that would have any real advantages in terms of monitoring or determining safety of these products, whereas on the flip side, Class II designation is the association between BIA-ALCL devices became more apparent, the manufacturers were able to be relatively nimble to put smooth devices on the market proceeding to a 510(k) or special 510(k) pathway wears if they were required to do a supplement that may of delayed access to the smooth expanders for patients with presumably a much lower cancer risk. You know, I think it's a trade-off here, but we have to consider the actual implications of what a Class III versus Class II designation would result. What are the advantages? What are the disadvantages?

Dr. Harris: Thank you. Dr. Ballman.

Dr. Ballman: As people were struggling trying to dissect the risk from the actual procedure versus the device, I'm really having a hard time dissecting between the expander and subsequent implant, which it happens in the majority of times. So, if it's made a Class III, again, they can monitor more, but I don't know if they're going to gain any additional information to know if it's do to the expander or if it's do to the implant, because I think there's been very few in breast only just expanders. And not subsequent implants. You know, I was told not to look at the other data where there are no sort of permanent implants that follow, but if you look at that data the argument is on the basis of that, we are going to make it a Class II. Again, I'm having a hard time seeing why this should be a Class III.

Dr. Harris: Thank you. Dr. Li. You are on mute, Dr. Li. Dr. Li, you need to unmute yourself. We can't hear you.

Dr. Li: Sorry.

Dr. Harris: There we go. Perfect. I want to bring this discussion back actually a little bit to the device itself. We have not actually discussed the performance of the device, and this gets to Dr. Bryant's question about separating the device from the procedure. In the literature summary that you provided us, the rate of [phone ringing] sorry. The rate of device failure was 30%. And the FDA identified the main device failures to be rupture and leakage. But yet none of the mechanical tasks that the FDA suggested would be used as special control actually address rupture and leakage. There is a disconnect between the test required by the FDA in their suggestion and the main modes of failure. If you're talking about something that is in for a short period of time, six months or less, the rupture rate is still 30% and there's actually no control for that or way to make that improve that's actually kind of an uncontrolled portion of the device,

and it's unclear then if the surgeon can or can't do anything to avoid those problems. I think one of the big unknowns here is why does the device perform really as badly as it does in terms of rupture and leakage?

Dr. Harris: Anyone on the panel able to comment about this issue of rupture and leakage? Dr. McGrath?

Dr. McGrath: I think that the ruptures are largely related to the fact that someone is sticking a needle into either the port or accidentally into some other portion of the expander during the expansion process. Don't forget it's filled repeatedly over a period of time. Maybe four, six, even eight times and it's possible that the damage is caused. That is I'm sure why that ranks as the number one device failure due to leakage. There is in the presentation you heard that they are asking for, you know, information about both the valve and the filler port in terms of their integrity and self sealing. If you go through the port correctly and hit the port, but there's no hope if you accidentally miss the port and stick your needle into the device. It's going to leak.

Dr. Harris: Thank you. Dr. Hunt?

Yes. Hi. Kelly Hunt. I just wanted to clarify from the data. I guess I interpreted that of the available data, 30% of the reported complications were those types of issues, but not the 30% of the time the tissue expanders are placed they have a failure or leakage because that is not at all my experience in clinical practice. That seems like a really, really high number. I interpret it as of the available studies, the studies reported that in patients who had complications 30% of the time it was related to that issue, but so, can someone clarify that? Thank you.

Dr. Dean: I believe your interpretation is correct Dr. Hunt.

Dr. Harris: Someone had their hand up. Dr. Bloom, you had your hand up and now it's

down.

Dr. Bloom: Matt Bloom, Los Angeles. I did table 5 of the literature provided to us. Exactly that. The complications are listed not as complication rates, but percentages of studies that mention that as a complication. So, it can be very misleading and the infection rate of 71%, for example.

Dr. Harris: So, are there any other comments relating to this question of classifying the tissue expanders as Class III? If not Class III, presumably Class II and why? I've heard mixed opinion. Some -- well, let me hear from Dr. Galandiuk.

Dr. Galandiuk: Well, a couple of comments. There were some comments made about the infection risk first by Dr. Bryant and others. I think you can't separate the procedure from the infection risk. I mean, they go together. But I think a big problem is many surgeons when they are implanting foreign bodies really don't discuss carefully with the patients the risk of infection and what happens when you have an infection in the presence of a foreign body, and that's whether you implant mesh or pacemaker or any kind of foreign body. And this has big consequences I think in this case because it can delay chemotherapy, start of radiation, in some cases require explants. I think that's a big thing and it still needs to be highlighted as a risk regardless of whether it's due to surgeons techniques. It has big consequences and I think it's not discussed often by the surgeon. Second, the item about the anaplastic lymphoma. I think we as surgeons implant many foreign bodies. You look at ports we infect. Artificial sphincters. Hickman's. Many different things, yet at least I'm not aware of anaplastic lymphoma being reported. Dr. Matarasso said with his estimates of 50,000 implants or expanders per year puts it at about a million and half I guess over 30 years. Still, if you think things in MAUDE I think are

very underreported. Most patients don't even know about MAUDE even existing. We don't know the real rate of this and I think you have to list that as a real risk and I think that still is a serious thing. I mean, you are still looking at even if you think it's vastly underreported, I think that is still a significant matter. I still would support listing this as three.

Dr. Harris: Great. Thank you. Dr. Armstrong.

Dr. Armstrong: Thank you. This is Debbie Armstrong. I think, as you heard, these are used so commonly that the hesitation of making this a Class III is whether that would impact in any way the patient's ability to be able to have access to these. And one of the things that could potentially be helpful is to know what happened when -- I don't even know when that happened, what year that happened, where the permanent implants went to a Class III. Was it difficult to getting access to these? Are we creating hurdles that, you know, we know what we would like. We would like to have every problem these people have reported, but I don't know if making that a Class III is going to have that happen. In fact, the sort of non-formal, you know, that advocate-based reporting system is giving more information than the regulatory information system. I don't think any of us want to put in hurdles that really aren't going to provide the information that we would really like to have provided. I guess one question I would ask the FDA is what happens when the permanent implants went to Class III? Were there shortages? Was there difficulty for getting access to these? I think that might be information that would be helpful for us.

Dr. Dean: I would like to defer that question to Dr. David Krause.

Dr. Harris: Dr. Kraus?

Dr. Krause: Yeah. Sure. Sorry. It took me a couple of seconds to find my mute button.

Yeah. Thanks for the question. We unclassified breast implants, and that was silicone gel filled and the saline implants in 1988. The call for PMA's for the silicone gel filled implants was not sent until 1991 and the FR notice to ask for PMA's for the saline breast implants was not sent until 1999. So, it didn't happen right away. There's usually a delay. Also, in 1992 when the moratorium on silicone gel breast implants was put in place, they did make arrangements so that patients who needed reconstruction could get silicone gel filled breast implants if that was the best device for that use at the time by entering into what was called and adjunct study. So, there were ways to accommodate patients and my feeling is the FDA would certainly do a check for shortages and make sure that necessary devices were available. I hope that answers your question.

Dr. Harris: Thank you. Ms. Block.

Ms. Block: First of all, Renata Block, physician assistant. I appreciate everybody's input and everybody has made amazing points in regards to this. I, too, am between the Class III and Class II and trying to find a justification of placing this in either category. Based on what I have been listening to, Dr. Armstrong, thank you, for bringing up the breast implants going from Class II to III. I feel that this eventually is going to be a Class III. Just because they are surgically placed and they are often times left in longer than the six month duration that is recommended, but we also have to look at the cause and effect. As far as someone mentioned in regards to, is it the surgeon or is it the actual implant? It's kind of both. I mean, we have to put in the implant and the implant then may have a cause and effect of the outcome. And again, that can be determined by the surgeon what is needed at the time for the implant. Based on the data that I have been listening to, I believe that a Class III is justifiable. And also, on the definition of the Class III

compared to the Class II. Substantial importance of preventing impairment of the human life or the device presents a potential unreasonable risk of illness and I know we were talking about the definition of that, but with the data that was presented, I feel Class III is reasonable. Thank you.

Dr. Harris: Thank you. Well, we have a challenging agenda today. Unless there are some absolute additional burning comments, I would like to summarize from Dr. Dean. I think you've heard a range of comments. One common theme is that people certainly don't want to see access to these devices reduced as a result of any reclassification. I think people are all in favor of safety, but there's been legitimate concerns raised about what sort of additional information will be gained when looking at potentially very rare and infrequent events. I think the agency will need to take all of that into consideration when making their final decision here. So, unless anyone has a major objection, I would like to move on to question number three --

Dr. Dean: Dr. Harris? Actually, we would like a recommendation from the panel in general. It would be useful to know where each panel member falls on the recommendation of Class II or Class III.

Dr. Harris: Well, we'll just take a vote. Dr. McGrath. Two or three? Two? Okay. Dr. Ballman.

Dr. Ballman: I'm saying two because I don't think we are going to get any additional information due to implants happening right after the expanders.

Dr. Harris: Dr. Galandiuk.

Dr. Galandiuk: Class III.

Dr. Harris: Dr. DeLong.

Dr. DeLong: I agree with Dr. Ballman. Class II.

Dr. Harris: Dr. Matarasso.

Dr. Matarasso: Two.

Dr. Harris: Dr. Pusic.

Dr. Pusic: Three.

Dr. Harris: I think three?

Dr. Pusic: Three.

Dr. Harris: Thank you. Dr. McCarthy.

Dr. McCarthy: Three.

Dr. Harris: Dr. Seidman.

Dr. Seidman: Before I respond, I thought I was a non-voting member before I throw my number out there. Three.

Dr. Harris: Thank you. Dr. Hunt.

Dr. Hunt: Three.

Dr. Harris: Dr. Li.

Dr. Li: Three.

Dr. Harris: Dr. Soucek.

Dr. Soucek: Two.

Dr. Harris: Dr. Seidman.

Dr. Seidman: Three.

Dr. Harris: Dr. Bloom.

Dr. Bloom: One half rounds up to three.

Dr. Harris: Miss Agazie. I hope we didn't lose her again. Ms. Block.

Ms. Block: Three.

Dr. Harris: Dr. Bryant.

Dr. Bryant: Two for the reasons I discussed, and also potential impact it would have to the definition of reasonability for the entire surgery platform that provides products to much more than just this particular topic.

Dr. Harris: Ms. Brummert.

Ms. Brummert: Class III.

Dr. Harris: And Ms. Fisher.

Ms. Fisher: Two.

Dr. Harris: My apologies I may have called upon people who are not voting members. I apologize, but good to hear your opinion regardless. Dr. Dean, is that sufficient for you?

Dr. Dean: Thank you. I would like to circle back to the earlier question, but I don't think we actually had you confirm. It sounds like from the panel's discussion, there is an agreement that there is a reasonable expectation of effectiveness for these devices.

Dr. Harris: Yes. I believe so.

Dr. Dean: Thank you. That is sufficient.

Dr. Harris: Great. We'll move on to question number three. FDA, if you could read that question for the panel.

Ms. Ki: Question three. If you agree with the risks about tissue expanders intended for use in the breast, please discuss whether these risks would also apply to other tissue expanders intended for use in the breast regardless of technological characteristics.

Dr. Harris: Okay. I'm not sure I understand that question. You are saying other tissue expanders for the breast is a question? Can we see that question one more time, please? So, I don't understand.

FDA: No. Apologies. These are for tissue expanders that are used in parts of the body other than the breast.

Dr. Harris: Other than the breast. There we go. This was simply a test to see if we were paying attention. This now we are saying should we apply the same risk assessment and classification for tissue expanders placed in locations other than the breast. We can take the question down, please. All right. Any comments? Dr. Armstrong.

Dr. Armstrong: I would agree with one of the comments that came up before which is I think the fact there is such limited data on these being used on other sides of the body that whatever decision is being made for the breast implants should apply to these implants used in other sides of the body. Just because it is so rarely done, if we are really concerned about a rare side effect then we should be concerned about it wherever this implant is being used. Even though there's not data to raise a concern, I think this just hasn't been used enough to know whether, particularly the lymphoma concern, is applicable there. I would advocate that whatever decision is made for the implants used in the breast should be used for the implants elsewhere.

Dr. Dean: Apologies. I actually skipped to a different question there and I was thinking about this. This is for any expanders that use other technologies, but also used in the breast. My apologies.

Dr. Harris: Okay, So, can we hear any examples of those or maybe some of the panel members are familiar with other types of tissue expanders that are not using saline injections? I guess there was one mentioned about injection of gas or carbon dioxide. Are there others that people can tell us about briefly? Dr. DeLong.

Michael DeLong: I don't have any personal experience with these, my understanding is they have a capsule inside you can have them remotely inflate while inside the patient body. I would agree that they should mirror whatever the class designation is for standard tissue expanders. They are arguably more complex. LCJ goes to three, they should be three for sure.

Dr. Harris: Okay. Any other comments? Dr. Bryant? Yes, please.

Dr. Bryant: Dr. Lamont Bryant. I agree that whatever classification for one should be for the other. As I understand it those products are Class II and I guess my question would be if the safety, if the track record is consistent with the rarity that we see for the previously discussed product, then I would still say two, but can you help us understand what the safety and effectiveness PROFILE for those products are?

Dr. Dean: I don't have this information. David, would you like to comment on this? Dr. Krause may not be available. So, I --

Dr. Krause: No. I'm here. Sorry again. I'm slow on the clicker. As far as I know, the Aeroform product is not being marketed, and so there's very little data, if any, except for the original study that we used in order to grant the de novo. and since then I don't think any MDRs

have come in and I don't think any product has been sold, but that's what I know. Somebody may have different information. It is the only one as far as I know, and so if there's no data on that one, there would be no data on any others.

Dr. Harris: Okay.

Dr. Dean: I believe this is a general question just to get your input on any type of tissue expanders use in the breast regardless of technology. With the same risks, do you think apply?

Dr. Harris: I think it's a bit of a speculative question, because I would think that someone would have to do the material chemistry of the device itself and its interface with the host but Dr. DeLong, any comments?

Dr. DeLong: I was just going to say exactly what you said. Right now they all have a silicone shell. Our understanding is that BII reaction is somehow related to silicone. It still comes up to the tissue expander -- pick another material. Whether or not we can say those risks necessarily apply, but I think in that case then you would make them go through, if it's Class III PMA anyway they need to generate medical data. It seems like in order to know whatever you addressed those additional risks to safety and effectiveness is the updated for new technological characteristics.

Dr. Harris: Dr. Armstrong.

Dr. Armstrong: Sorry. I was pretty much going to say what Dr. DeLong said, which is in preclinical studies it looks like it's going to be less immunoreactive and looks promising. I think you would still need when it's initially used you would want to meet the same criteria as other implants and maybe that can be moved to a lower class at some point in time, I

think I would agree initially it probably should stay at the same class as the current family of tissue expanders.

Dr. Harris: Dr. Bryant.

Dr. Bryant: To revisit my earlier statement Dr. Clouse has clarified. I assume the conversation was specific around these products, but again, I agree with Dr. DeLong if there is a new material, of course, we are going to have to qualify that. That probability be a Class III. But for the data that we've had and will be seen with the previous topic the rarity, I still say for Class II for that and this, depending on the material.

Dr. Harris: So, Dr. Dean, is that sufficient?

Dr. Dean: Yes, that is. Thank you very much.

Dr. Harris: We can move on to question number four if the FDA will read that to the panel.

Ms. Ki: Moving on to tissue expanders intended for use in other parts of the body or non- breast use. Question four. FDA has identified the following risks to health for tissue expanders intended for use in other parts of the body or non-breast. The risks are skin trauma, device malfunction or device failure leading to reoperation, infection, adverse skin reaction, and pain or discomfort. Please comment on whether you agree with inclusion of all the risks in the overall risk assessment of tissue expanders intended for use in other parts of the body, or non-breast, under product code LCJ. In addition, please comment on whether you believe that any additional risks should be included in the overall risk assessment of these tissue expanders intended for use in other parts of the body, or non-breast.

Dr. Harris: I'm going to begin by saying I think we began to address this question perhaps prematurely. I think everyone was leaning, at least those who spoke, were leaning towards the idea that the risk assessment should be the same irrespective of the location in which the expander is placed. Is there someone who would like to add to that or disagree with that summary? Dr. DeLong.

Dr. DeLong: I would just comment that yeah, I don't think, you know, given that these are mechanistically unclear how BII or BIA-ALCL develop and we have no real strong data to suggest that it's specific breast tissue that causes it. I think we have to assume that these risks exist for tissue expanders placed somewhere else.

Dr. Harris: Thank you. Dr. McGrath?

Dr. McGrath: I was just going to comment that I think that used elsewhere the expander's used in a very different way. In general, it's a shorter period of time that they are in. The patient very often, particularly if you're doing a child with a giant hairy nevus or a burn patient, there's no question of adjuvant therapy that will be brought into the picture. And I think that these devices are so diverse. I don't know how -- and you use them for so many applications in so many parts of the body, including, you know, just putting it in sometimes to expand what eventually will be autologous tissue flap that you want to make bigger so you have more to move. I think it would be very difficult to sort this out. And again, to get any information about whether the devices, which rarely are in for six months at all, whether you're going to be able to do a study to determine that ahead of time would be very difficult or impossible. So my strong feeling on these is to treat them as surgical instruments that you're using and put them into a two category.

Dr. Harris: Okay. Sounds like we are in store for a little quick vote. So, we'll start with Dr. McGrath, who voted two. Dr. Ballman, your thoughts.

Dr. Ballman: It should be whatever we do with the breast expanders.

Dr. Harris: Okay. Dr.Galandiuk.

Dr. Dean: Just I apologize for jumping in here. Actually, we will get to that question, but this particular question is asking you about the risks associated with device tissue expanders used in parts of the body other than the breast.

Dr. Harris: So, I think that, at least my interpretation that Dr. McGrath's comments are that those risks vary quite widely based upon different uses, different constructs, etc. Any other comments in direct response to Dr. Dean's clarification?

Dr. Galandiuk: I would think that there is such varied uses that I don't really think you can comment on them and I think they should be bundled together with the breast uses or have the same risk stratification.

Dr. Harris: Any other thoughts on that? Dr. Pusic. Oops.

Dr. Pusic: Sorry. One quick comment because Dr. McGrath got me thinking about this as well. I worry about the unintended consequences of these changes and we all want to optimize safety, but I worry so much about access. These tissue expanders that are used in other areas of the body do come in a much greater variety of shapes and sizes and because they maybe rectangular and they are and I just am thinking through the implications of if they become Class III that that might impact availability because it may be very difficult to then study each of these different subtypes because, again, the variety is much greater.

Dr. Harris: Dr. Soucek.

Dr. Soucek: Can you hear me?

Dr. Harris: Yes.

Dr. Soucek: I wasn't sure if you could hear me before. I have a reticence to vote on something without any -- or give an opinion without any data really supporting it. It just doesn't make me feel like we are on solid ground. But the second thing, there is an inference of time that the implant or the expander stays in versus risk. And so, can somebody address that for me? Because for breast expanders, that would be precursors to implants for the breast. You know, it's more than six months. It could be eight months or whatever. In some of these other usages, it's just very short, so I don't know that we really want to come down really hard on something like that. So, that's my thought.

Dr. Harris: Thank you. Any comments to Dr. Soucek's comments or thoughts? Well, Dr. Dean, simple sounding question. But I don't think there's a simple answer or consensus in large part because we are talking about a broad range of devices, broad applications, and even less information than we have for the tissue expanders used for breast. So, I don't know how helpful that will be, but I can't think of a more concise summary. If anyone else can, please.

Dr. Dean: You've given us information to think about regarding the risks associated with these devices. I think we can move on to the next question. Thank you.

Dr. Harris: Great. So, the FDA will read I believe it's question number six or five. I lost track.

Ms. Ki: Question five. Section 513 of the food, drug, and cosmetic act state that a

device should be Class III if insufficient information exists to determine that general controls and special controls are sufficient to provide reasonable assurance of it's safety and effectiveness and the device is purported or represented to be for a use in supporting or sustaining human life, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury. A device should be Class II if general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness and there is sufficient information to establish special controls to provide such assurance. A device should be Class I if general controls sufficient to provide reasonable assurance of the safety or effectiveness or sufficient information exists to determine that general controls are sufficient to provide reasonable assurance of the safety of effectiveness or establish special controls to provide such assurance, but it is not purported or represented to be for use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health and does not present a potential unreasonable risk of illness or injury. FDA believes general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness and sufficient information exists to establish special controls to adequately mitigate the risks to health and provide reasonable assurance of device safety and effectiveness for this device type. As such, FDA believes that Class II is the appropriate classification for tissue expanders intended for use in other parts of the body or nonbreast. Following is the risk and mitigation table, which outlines the identified risks to health for these devices and recommended controls to mitigate the identified risks. The risk mitigation recommendations for tissue expanders intended for use in other parts of the body, or nonbreast, under product called LCJ are the following. To mitigate the risk of this adverse tissue reaction, we recommend biocompatibility, evaluation, and labeling. To mitigate the risk of skin trauma, we

recommend performance testing and labeling. To mitigate the risk of reoperation resulting from device malfunction or device failure, we recommend performance testing and labeling. To mitigate the risk of infection, we recommend stabilization testing, validation information, shelf life validation, and labeling. To mitigate the risk of pain or discomfort, we recommend labeling. Please discuss whether the identified special controls for tissue expanders intended for use in other parts of the body or nonbreast appropriately mitigate the risks to nonhealth or whether additional or different special controls are recommended. The first three special controls are one, the patient contacting performance of the device must be demonstrated to be biocompatible. Two. Performance data must demonstrate the sterility of patient contacting components of the device. Three. Nonclinical performance testing must demonstrate that the device performs as intended under anticipated controls of use. The following performance characteristics must be tested. A. Mechanical assessment of the shell, including tensile strength, percent elongation, tensile set, and joint testing. B. Shell surface characterization, including manufacturing methods, surface roughness or texturing. C. Injection site testing to show that tissue expander can be accurately assessed. Accessed. D. Valve competency testing if applicable to demonstrate that the valve integrity is maintained at in vivo loads. And E. Self sealing patch testing if applicable to demonstrate a punctured patch can self seal and maintain that seal for the duration of use. The last two special controls proposed are number four, performance data must support the shelf life of the device for continued sterility, package integrity, and functionality over the requested shelf life. Number five. Labeling must include A, information on how the device operates and the typical course of treatment. B. Warning related to use beyond tissue tolerance, which may result in tissue damage. C. The risks and benefits associated with the use of the device. D. Postoperative care instructions. E. Alternative treatments. And F. Shelf life.

Dr. Harris: Okay. So, question five is basically asking if those special controls are sufficient for tissue expanders to be used in locations other than the breast and its biocompatibility, sterility, nonclinical testing, shelf life, and labeling. Any thoughts, questions, comments? So, I'm assuming by -- oh, Dr. DeLong.

Dr. DeLong: Sorry. Are we talking about class designation and how this is assigned or are we specifically talking about just the special controls and risks?

Dr. Harris: Well, special controls by definition would be a Class II device.

Dr. DeLong: Right.

Dr. Harris: And so, we are asking if these special controls do you think are sufficient to ensure adequate safety and effectiveness for these devices?

Dr. DeLong: I guess I would just kind of say what I said again. You know, I think one of the cases in the PROFILE registry is a patient who had a textured breast implant put in the gluteal region for augmentation from what I recall. So, there's nothing specific to the breast. For these risks, I think the reason we are seeing it in the breast is because those expanders can be textured or implants for that matter, and they are just much more common. So, if we think that, you know, a Class III designation in those risks are appropriate for tissue expander used in the breast, I think that, you know, basically whatever we say for designation for the breast I think should be for everywhere because those risks are -- we just pick it up more in the breast because there's just a lot more of them.

Dr. Harris: Okay. Other thoughts or comments? Dr. Soucek. Are you on mute?

Dr. Soucek: The one interesting to me -- can you hear me now?

Dr. Harris: Yes.

Dr. Soucek: Good. Is the self-sealing. You know, the mechanical testing was kind of specific. The self-sealing might want to be specific in terms of, you know, internal pressure. If you are blowing something up, self-healing is going to be dependent on how much internal pressure there is or as you add more fluid or whatever as you expand. So, it may self-heal in the beginning, but not so well at the end. There's going to be a cut off. At any rate, that's just thought.

Dr. Harris: I believe those special controls would require the manufacturer to demonstrate that the device does self-seal under its intended specifications or use scenarios. So, that would assumedly be contained in that data. Any other comments? Ms. Block.

Ms. Block: I just have a question for clarification between the classes. What you are saying is a Class II does have the special controls and what I'm hearing -- and correct me if I'm wrong, is Class III would not. Is that correct?

Dr. Harris: As I understand it, the Class III would suggest that there isn't sufficient information available to identify special controls that would then allow you to feel that there is reasonable safety and efficacy of this device, so you are then going to have to do studies that extend beyond special controls. That's my interpretation. Dr. Dean, correct me where I'm wrong.

Dr. Dean: Special controls allow us to have -- allow devices on the market that are substantially equivalent to predicates through the 510(k) process. If we do not feel that those special controls are sufficient to protect patient safety, then we require a PMA, that pre-marketing application.

Ms. Block: Thank you for the clarification. So, based on that, I mean, I think these

special controls are adequate, but based on my evaluation, I feel very strongly, like Dr. DeLong said, that we should follow suit with the breast implants and personally I think they should be a Class III. So, that would not take this into consideration is what I'm understanding.

Dr. Harris: Okay. Dr. McCarthy.

Dr. McCarthy: Thank you. Colleen McCarthy. I just wanted to reiterate what Dr. DeLong said. There are case reports of devices causing ALCL elsewhere in the body. PROFILE does not collect nonbreast cases of ALCL, and so as such, there's no systematic way to collect these cases. And so again, I support the idea that whatever we do with the breast tissue expanders we should do with tissue expanders elsewhere in the body.

Dr. Harris: Any other comments? So, Dr. Dean, it sounds like the majority of people feel what's good for the goose is good for the gander. Whatever we do for breast expanders we do for expander devices for other locations. Though the point was made that given they are used less frequently and there's so many more, there is concern voiced about whether that might prohibit the development and access to those devices since it might not be as commercially viable for a manufacturer.

Dr. Dean: I would like to make sure that all voices weigh in on this. Would it be possible to go around and ask the panel to vote whether or not they feel that these special controls are sufficient or if this should be Class III?

Dr. Harris: Absolutely. Dr. DeLong.

Dr. DeLong: I just had one quick question. How many of these devices are used? Would they qualify potentially as a humanitarian device? I mean, they are relatively rare.

Dr. Dean: I don't know the answer to that question. I can look into it.

Dr. DeLong: Okay. Because that can be another option to maintain access to these since it's a pretty low population.

Dr. Krause: To clarify -- this is David Krause. The humanitarian use device regulations now specify that it would have to be used less than 8,000 times a year.

Dr. Harris: Okay. So, Dr. DeLong, since you were just speaking, special controls adequate or should this be a Class III?

Dr. DeLong: It sounds like the panel was favoring Class III for the breast expanders, so I guess Class III. Whatever for the breast expanders. Same thing.

Dr. Harris: Dr. Ballman.

Dr. Ballman: As I voted before, I believe that whatever it is for the breast expanders I think should be for this.

Dr. Harris: Dr. McGrath.

Dr. McGrath: I think it should be a Class II. I think it will be exceptionally difficult to sort them out because first of all, I don't think they are that rarely used in other parts of the body. If you work at a burn center or if you work at a pediatric hospital, you're using these devices quite frequently. They are used in all age groups from children from the age of two to very old people with, you know, pressure soars and so forth. They come in such a variety of, as Dr. Pusic mentioned, shapes and sizes. To look at all these would be extremely difficult. The uses are so myriad and the complication rates vary so much with just details, such as the part of the body they are used on. They do much better if you're putting it under a robust soft tissue. If you're

trying to expand over the shin, they are going to perform very poorly because the skin is tight and thin. To get this sorted out for all of these devices and still, I don't know how you could do it. Since I don't think we have to have a rule of consistency just because we chose one thing for the breast. These devices, as I mentioned before, stay for shorter periods of time. They are not generally associated with other adjuvant therapy and they are in and out and they are allowing you simply to do an operation that you were going to do anyway to try to cover a wound or remove a tumor and cover it or take off a burn scar. And my feeling is that the special controls look really good and I personally vote for Class II.

Dr. Harris: Thank you. Dr. Galandiuk.

Dr. Galandiuk: I would vote for Class III in agreement with Dr. DeLong's comments.

Dr. Harris: Dr. Matarasso.

Dr. Matarasso: Two.

Dr. Harris: Dr. Pusic. Dr. Pusic comes back. Dr. McCarthy.

Dr. McCarthy: Three.

Dr. Harris: Dr. Seidman.

Dr. Seidman: Three.

Dr. Harris: Dr. Armstrong.

Dr. Armstrong: Sorry. Three.

Dr. Harris: Dr. Hunt.

Dr. Hunt: Three.

Dr. Harris: Dr. Li.

Dr. Li: Three.

Dr. Harris: Dr. Soucek.

Dr. Soucek: Two.

Dr. Harris: Dr. Diegelmann.

Dr. Diegelmann: Three.

Dr. Harris: Dr. Bloom.

Dr. Bloom: Three.

Dr. Harris: Miss Agazie. You are on mute, Miss Agazie. Show me with the fingers, two or three. Three. Perfect. Ms. Block.

Ms. Block: Three

Dr. Harris: Dr. Bryant.

Dr. Bryant: I will say whatever we decide for the tissue expanders. And I don't remember us deciding it. I thought it was a mixed. So, whatever we decide for the expanders

Dr. Harris: Miss Brummert.

Ms. Brummert: Class III.

Dr. Harris: Miss Fisher.

Ms. Fisher: Two.

Dr. Harris: Alright, Dr. Dean.

Dr. Dean: Thank you. We appreciate your input on the proposed special controls and the classification. I think we can move to the next question.

Dr. Harris: Okay. We're going to move on to question six, please. FDA read.

Ms. Ki: Question six. Please discuss whether you agree with FDA's proposed classification of Class II with special controls for tissue expanders intended for use in other parts of the body, or nonbreast. If you do not agree with FDA's proposed classification, please provide your rationale for recommending a different classification.

Dr. Dean: I think we have just covered that.

Dr. Harris: So, do we need to go further? Or we're okay? Dr. Dean?

Dr. Dean: I believe that is sufficient that we know your classification. Thank you.

Dr. Harris: Move to question seven.

Ms. Ki: Now, we'll discuss tissue expander assessments. Question seven. FDA has identified the following risk to health for tissue expanders accessories. The risks include skin trauma, device malfunction leading to increased operative time, infection, adverse tissue reaction, and pain or discomfort. Please comment on whether you agree with inclusion of all the risks in the overall risk assessment of tissue expander accessories under product code LCJ. In addition, please comment on whether you believe that any additional risk should be included in the overall risk assessment of these tissue expander accessories.

Dr. Harris: Okay. So, any questions or comments about that question? Dr. Li? You are on mute.

Dr. Li: Sorry. I hit it by mistake.

Dr. Harris: No problem. Oh, I see. You didn't have a comment. Okay. Any thoughts? Anyone? I thought there was a comment earlier questioning why we would be doing differential risk assessments for the accessories versus the expanders. I thought that was actually a comment of Dr. Ballman's. Am I misquoting you? Okay. Alright. My mistake.

Dr. Ballman: Yeah. I'm sorry. We are talking about the accessories now, right?

Dr. Harris: Correct.

Dr. Ballman: Yeah. I did not make any comment about the accessories.

Dr. Harris: Do you have any thoughts on the accessories while I have you on the spot?

Dr. Ballman: This is Karla Ballman. I mean, I think for the accessories I'm comfortable with it being Class II. You know, it's -- yeah.

Dr. Dean: I believe this question is on the risk for the - -

Dr. Ballman: The risks, yeah. I think the risks are well defined as stated. Karla Ballman again.

Dr. Harris: Does anybody have any comments or concerns about the risks? Dr. Bryant.

Dr. Bryant: Again, the question I articulated earlier. Procedure, which is a product, and, again, I know procedure is different because it's not left in, but that would be the only thing I would [indiscernible].

Dr. Harris: Any other thoughts or comments? So, this is really a discussion regarding the risk assessment for the accessories used to insufflate and service these tissue expanders. Are there any risks that somebody feels are either inappropriately stated or are missing? If not, it

sounds like the committee agrees with the risk as outlined.

Dr. Dean: Thank you. That is sufficient.

Dr. Harris: Okay. We'll move onto the next question, please.

Ms. Ki: Question eight. Section 513 of the Food, Drug, and Cosmetic Act states a device should be Class III if insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of its safety and effectiveness and the device is purported or represented to be for use in life supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health or if the device presents a potential unreasonable risk of illness or injury. A device should be Class II if general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness and there is sufficient information to establish special controls to provide such assurance. A device should be Class I if general controls are sufficient to provide reasonable assurance of the safety and effectiveness or insufficient information exists to determine that general controls are sufficient to provide reasonable assurance of the safety and effectiveness or establish control, establish special controls to provide such assurance, but is not purported or represented to be used in supporting or sustaining human life, or for a use which is of substantial importance in preventing impairment of human health and does not present a potential unreasonable risk of illness or injury. FDA believes general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness and sufficient information exists to establish special controls to adequately mitigate risk to health or provide reasonable assurance of device safety and effectiveness for this device type. As such, FDA believes that Class II is the appropriate classification for tissue expander assessments. The

following is the risk mitigation table which outlines the identified risks to health for these devices and the regular controls to mitigate the identified risks. The risk mitigation recommended for tissue expander accessories under product code LCJ are the following. To mitigate the risk of skin trauma, we recommend performance testing and labeling. To mitigate the risk of increased operative time due to device malfunction, we recommend performance testing and labeling. To mitigate the risk of infection, we recommend sterilization testing and validation information, shelf life validation, and labeling. To mitigate the risks of adverse tissue reaction, we recommend biocompatibility, evaluation, and labeling. To mitigate the risk of pain or discomfort, we recommend labeling. Please discuss whether the identified special controls for tissue expander accessories appropriately mitigate the identified risk to health and whether additional or different special controls are recommended. Number one. The patient contacting components of the device must be demonstrated to be biocompatible. Number two, performance data must demonstrate the sterility of patient contacting component of the device. Number three. Nonclinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. Number four. Performance data must support the shelf life of the device for continued stability, package integrity, and functionality of the requested shelf life. Number five. Labeling must include one, information on how the device accessory operates. Two, the risks and benefits associated with the use of the device accessory. And three, shelf life.

Dr. Harris: Okay. So, any thoughts or comments from the panel? Is there anyone who feels that these special controls are inadequate? Do we feel that they are sufficient to reasonably assure safety and efficacy of these accessories? So, Dr. Dean, do you want to hear from each panel member or are you satisfied that the panel is content with these special controls as outlined?

Dr. Dean: I would like to ask, does anyone disagree with a Class II designation for these accessories and the special controls?

Dr. Harris: Anyone?

Dr. Dean: I will take that as unanimous agreement. Thank you. That's sufficient.

Dr. Harris: Great. So, now, to our final question number nine.

Ms. Ki: Question nine. Please discuss whether you agree with FDA's proposed classification of Class II with special controls or tissue expander accessories. If you do not agree with FDA's proposed classification, please provide your rationale for recommending a different classification.

Dr. Dean: I believed I jumped the gun a little bit since we were talking about special controls, but I believe I have the answer. The panel unanimously supports Class II. Thank you.

Dr. Harris: Right. Great. Well, thank you, everyone. We are going to take a lunch break. We are running a little behind, but I would like everyone to come back -- it is almost 1:00. So, maybe by 1:30 p.m. Eastern Standard Time. That will give you just over 30 minutes. Thank you. We'll see you in 30 minutes.

LUNCH BREAK

Dr. Harris: Good afternoon. We are going to resume the panel meeting. At this time, I would like to invite the FDA to start their presentation. I would also like to remind the public observers at this meeting that while the meeting is open for public observation, public attendees may not participate except at the specific request of the panel chair. FDA, you may now begin your presentation.

Ms. Ki: Good morning. My name is Tajanay Ki and I am a Lead Reviewer in the Division of Infection Control of Plastic Surgery Devices within the Office of Surgical and Infection Control Devices and CDRH's Office of Product Evaluation and Quality. Today, I will presenting information regarding our effort to classify mammary sizers regulated under product code MRD. These devices are currently unclassified and we are looking for your thoughts and recommendation on the appropriate regulatory classification for these devices. This is an outline for my presentation. These are the items that we will be discussing today.

Mammary sizers, also known as breast implant sizers, are designed for temporary intraoperative placement in the breast pocket to assist in determining the desired breast implant shape and size for the patient prior to implantation of a breast implant during breast augmentation or breast reconstruction procedures. Mammary sizers are generally constructed with an elastomeric outer shell and can be filled with either silicone gel or saline. The filling material can be pigmented to help differentiate mammary sizers from breast implants. Mammary sizer's are available in a range of diameters, projections, and volumes to match the range of breast implants they intend to approximate. Some mammary sizers are intended for single use, while others may be re-sterilized and reused. All mammary sizers are meant for temporary use during the surgery. They are not intended to remain implanted in the body.

Indications for use identify the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended. Mammary sizers are indicated for temporary placement during breast augmentation or reconstruction procedures to assist the surgeon in determining the appropriate size, shape, or volume of the long-term breast implants.

Mammary sizers are a pre-amendment unclassified device type. This means that this device type was marketed prior to the Medical Device Amendment Act of 1976. It was not classified by the original classification panels. Currently, these devices are being regulated by the 510(k) pathway and are cleared for marketing if their intended use and technological characteristics are substantially equivalent to a legally marketed predicate device. Since these devices are unclassified, there is no regulation associated with the MRD product code. To date, a total of 11 510(k)s have been approved by the 510(k) pathway under the mammary sizer product code MRD. Please refer to section 2 of the executive summary for a complete list of cleared devices under product code MRD.

The mammary sizer may be used in patients who are undergoing breast augmentation or reconstruction surgery. It is used to evaluate the appropriate mammary prosthesis, or breast implant, volume intraoperatively before the prosthesis are placed. The device is a tool to aid in surgical decision making only during surgery. An alternative treatment option is to conduct the breast augmentation or reconstruction surgery without the use of a mammary sizer with the surgeon determining the breast implant size using their clinical judgment.

We conducted a literature review to identify any published information between April 1, 2012 and April 1, 2022, regarding the safety and effectiveness of mammary sizers. Searches were limited to publications in English and excluded laboratory studies, animal studies, economic and cost-effective analyses, nonclinical trials, case series, and case reports. After an initial yield of 1,234 articles, articles not related to breast implant sizers were removed based on a review of the title and abstracts. This yielded 22 literature references. After reading the 22 articles, a total of three articles were selected for review based on their relevance to the reported safety and/or

effectiveness of these devices. The three articles were reported on their retrospective study design. Two articles, the Kim and Wang articles did not report adverse events associated with mammary sizer use. One study, the Khoo study, compared the outcome of cases that employed the use implant sizes versus those that did not use breast implant sizers. The study reported that the group that used the mammary sizer was associated with a higher total a complication rate when the permanent implant was placed compared to the no mammary sizer group.

However, there were some limitations with the study, including if complication rates were truly based on sizer use. Mammary sizers are intended to be used intraoperatively to assist the surgeon in determining the size of the appropriate breast implant to use. In the three articles, breast implant sizers were used intraoperatively. However, the articles did not describe the overall effectiveness of the device. All three studies evaluated different outcomes associated with mammary sizer use. The first report evaluated a comparison of complications between two groups of using a mammary and sizer and implant incision through a funnel versus using a mammary sizer and implant incision without the funnel. A second report evaluated use of mammary sizers and nipple sparing mastectomies and reconstruction. The third report evaluated mammary sizers in routine use compared to nonuse.

The quality of evidence for the systematic literature review is low since only three studies met the search criteria. The reported studies were retrospective. All studies were conducted outside the US. Two of the three studies had a low sample size and all three studies evaluated different outcomes associated with mammary sizer use. The next three slides provide background information for medical device reports, or MDRs. For the sake of time, I will not go through this information in detail since this information was summarized previously in a presentation for

tissue expander accessories under product code LCJ. This is a continuation of the MDR background and a reminder of how MDRs can be used. This is a continuation of the MDR background and a reminder of the limitations.

To further contribute to the benefit risk assessment of mammary sizers, the agency reviewed individual MDRs to identify adverse events related to the use of mammary sizers in product code MRD. Entered through April 1, 2022, the search identified 107 relevant MDRs. The 107 MDRs included 55 malfunctions and 52 serious injuries. Note that the individuals submitting the MDR chooses a category for the event type be it serious injury, malfunction, or another category. There were 52 MDRs submitted as serious injuries. Of these serious injuries, 19 report the sizer rupture. 17 MDRs reported the rupture occurred while the device was inside the patient. In some cases, necessitating manual use of silicone gel and two MDRs reported that the device did not come in contact with the patient. Mammary sizers are available as single use or resterilizable. It is not clear if the risk of rupture is the same for single use mammary sizers or mammary sizers that have been resterilized. Of the 19 MDRs reporting rupture, 12 reported that the breast implant sizer is a style that can be resterilizable, and four do not provide information regarding the sterilization and three report that the sizer is not resterilizable. 18 MDRs report that the surgeon failed to remove the sizer and exchange it for a breast implant. 10 MDRs contain both the implant and explant date. The shortest time to explant was one day and the longest is four years. It is unknown and unreported why the sizer was left in the patient for that long. There are two reports of systemic symptoms or breast implant illness. One MDR identified the use of breast implant after the sizers and the second report does not provide any information regarding additional device use.

There were 55 MDRs submitted as device malfunction. Note, as individuals submitting the MDR chooses the event type, there may be similar adverse events identified under the serious injury and malfunctions. Of these device malfunctions, 25 MDRs report their sizer ruptured. 12 MDRs reported the rupture occurred while the device was inside the patient in some cases necessitating manual silicone gel remover. Five MDRs reported the device did not come in contact with the patient and eight MDRs do not provide any information. Of the 15 MDRs reporting foreign body on the sizer, 11 MDRs reported a grit like plastic particles. The devices were new or out-of-the-box and in all 11 reports, the devices were washed and used in the procedure. And four MDRs reported out-of-the-box contaminants, including hair and cellophane.

Of the three MDRs reporting failure of the sizer to be removed and replaced with a breast implant, two MDRs do not include the implant or explant date. And one MDR reported the sizer remained implanted for 18 years. Of the three MDRs reporting greasy residue after re-sterilization, two MDRs reported the manufacturer confirmed facility performed cleaning or sterilization correctly. And the manufacturer in one MDR reported the occurrence of residue as described in the device labeling as a known potential adverse event. Overall, the MDR analysis shows that there are complications reported with the use of breast implant sizers. Please refer to section 6 of the executive summary for the specific details of the MDR analysis.

This slide provides background information for recalls in the medical device recall database. For the sake of time, I will not go through this information in detail since it was summarized previously in the presentation for tissue expanders and accessories under product code LCJ. A review of the medical device recall database identified four recalls. One Class III recall was initiated due to error in labeling, which resulted in the two barcodes in the breast

implant and mammary sizers being unreadable by a GS1configured scanner. One Class II recall was initiated due to expired mammary sizers being shipped to users. One Class II recall was initiated due to certain mammary sizers that were packaged with the incorrect instructions for use. And one Class II recall was initiated due to error in labeling, which resulted in certain 380cc mammary sizers being labeled as 330cc mammary sizers. The definition of a Class III and Class II recalls can be found on page 14 of the mammary sizer executive summary. These recalls are related to labeling errors do not suggest there are general safety concerns related to mammary sizer devices is a product class. To determine the appropriate classification for mammary sizers, we have identified risks associated with these devices and possible mitigations for these risks. We will be asking the panel for input on the list of risks and mitigations. To identify the risks of these devices, we reviewed MDRs recall information and the literature analysis, as previously discussed. And the information available to FDA regarding cleared devices.

Here are the four risk categories we've identified for mammary sizers. Adverse tissue reaction. Device materials may elicit adverse tissue reactions, such as allergic reaction, toxicity, and foreign body response. Infection. Inadequate device sterilization or packaging integrity may lead to infection leading to additional surgical procedures. Device malfunction leading to increased operative time. Device malfunction may result in rupture, gel bleed, and gel migration leading to increased operative time and additional risks, such as increased anesthesia. Use error/improper device use. This can result from the device accidentally remaining implanted and not exchanged for a breast implant. We believe general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness and sufficient information exists to establish special controls to adequately mitigate the risks to health and provide reasonable assurance of device safety and effectiveness for this device type.

Here is a table with identified risks, as listed on the previous slide, and the proposed mitigation measures, which are recommend to be addressed through special controls. To mitigate the risk of adverse tissue reaction, we recommend biocompatibility evaluation and labeling. To mitigate the risk of infection, we recommend sterilization testing validation information, reprocessing validation, shelf life testing, and labeling. To mitigate the risk of device malfunction leading to increased operative time, we recommend non-clinical performance testing and labeling. And to mitigate the risk of use error/improper device use, we recommend labeling.

Here is our proposed classification regulation for mammary sizers. Part A of the regulation defines the device as follows. A mammary sizer is intended for temporary intraoperative placement to assist in determining the desired breast implant shape and size for the patient. The device consists of an elastomeric outer shell that is filled with either silicone gel or saline. Mammary sizers are not intended for implantation. Furthermore, we are proposing these devices be classified as Class II devices with special controls. Based on the identified risks and recommended indication measures, FDA believes that the following special controls on the next two slides will provide reasonable assurance of safety and effectiveness for mammary sizers under product code MRD. Number one, nonclinical performance testing must demonstrate mechanical function and durability of the device. Number two, the device must be demonstrated to be biocompatible. Number three, performance data must demonstrate the sterility of the device. Number four. Performance data must support the shelf life of the device by demonstrating continued sterility and package integrity over the intended shelf life. And number five. Performance data must validate the cleaning and disinfecting instructions for reusable devices. And number six. Labeling must bear all information required for the safe and effective use of the device, specifically including the following. One. A clear description of the

technological features of the device, including identification of device materials, shapes, and sizes. Two. Information on how the device operates. Three. Validated methods and instructions for reprocessing if the device is reusable, including the number of times the device can be resterilized. Four. A warning against implantation of the device. Five. The shelf life. And six, disposal instructions. This concludes our presentation. Thank you for your time and attention.

You are on mute.

Dr. Harris: Thank you. So, now, we will take any clarifying questions that the panel may have for FDA regarding that specific presentation. Okay. Well, if there are no -- oh. Dr. DeLong.

Dr. DeLong: I was just going to clarify with the resterilization special control. You know, the MDR it seems like some of those reports there's a bit of a gel bleed being reported that there is some kind of sticky contents on the shell of the implant. Is it anticipated that this resterilization testing will include those gel bleed and infection sterility?

Dr. Harris: Dr. Dean?

Dr. Dean: I believe that the special controls will deal with both of those, yes.

Dr. DeLong: Okay.

Dr. Harris: Any other clarifying questions regarding the presentation? If not, then we'll move on to our panel questions and deliberations over those questions. So, if FDA will read the first question, and once again, I will remind everyone to state your name and make sure your microphone is unmuted when you make comments or ask questions. FDA?

Ms. Ki: We have the following questions for the panel. We are looking for your

thoughts and recommendations on the appropriate regulatory classification for these devices. Question one. FDA has identified the following risks to health for mammary sizers. Adverse tissue reaction, infection, device malfunction leading to increased operative time, use error/improper device use. Please comment on whether you agree with inclusion of all the risks in the overall risk assessment of mammary sizers under product code MRD. In addition, please comment on whether you believe that any additional risks should be included in the overall risk assessment of these mammary sizers.

Dr. Harris: So, do any of the panel members have a comment or question regarding these risk assessments? Are there any risks that we think are not adequately covered? Dr. Hunt.

Dr. Hunt: Yes. Hi. Kelly Hunt. Can I just ask? I mean, I think that if there's infection related to these, it seems like it's most likely related to improper use or them being in for longer than intended? Because the way that I've seen this used in the operating room is just, as it's sort of stated, as a sizer, so it's placed in and then taken out almost immediately. So, it seems unlikely that much of the risks that are listed there are really related to the use of the sizer, but, you know, as comments were made this morning about expanders and implants, I don't know how that you can really separate them if you're using a sizer and then you're putting in another device. But I do think that it could be related to improper use and I think that could be stated for just about any medical devices that we utilize as part of patient care. Thank you.

Dr. Harris: Thank you. Dr. Bryant, you had your hand up for a quick second.

Dr. Bryant: I did. LaMont Bryant. Dr. Hunt, thank you. I agree in addition, improper use or just the process of the procedure. Some of these adverse events could be associated with product versus procedure.

Dr. Harris: Any other questions or comments? So, to summarize, it seems as though the panel is content with the list of risks as outlined by FDA with no suggestions for added risk, but once again, emphasizing the blurred distinctions between procedural and device risk.

Dr. Dean: Hearing no additional risks, I will take that as unanimous agreement with the identified risks. Thank you.

Dr. Harris: Move on to question number two. If FDA will be so kind as to read that question for the panel.

Ms. Ki: Question two. Section 513 of the Food, Drug, and Cosmetic act states a device should be Class III if insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of its safety and effectiveness for that application of special controls would provide such assurance and the device is purported or represented to be for a use in supporting or sustaining human life, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury. A device should be Class II if general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness and there is sufficient information to establish special controls to provide such assurance. A device should be Class I if general controls are sufficient to provide reasonable assurance of the safety and effectiveness, or insufficient information exists to determine that general controls are sufficient to provide reasonable assurance of the safety and effectiveness, or establish special controls to provide such assurance, but is not purported or represented to be for use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, and does not present a potential unreasonable risk of illness or injury.

Question two. FDA believes general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness and sufficient information exists to establish special controls to adequately mitigate the risks to health and provide reasonable assurance of device safety and effectiveness for this device type. As such, FDA believes that Class II is the appropriate classification for mammary sizers cleared under product code MRD. The following is a risk mitigation table which outlines the identified risks to health for this device type and the recommended controls to mitigate the identified risks. The identified risk to health include adverse tissue reaction, which we recommend be mitigated through biocompatibility evaluation and labeling. Infection, which we believe can be mitigated through sterilization testing/validation/information, reprocessing validation, shelf life validation, and labeling. Device malfunction leading to increased operative time, which we recommend be mitigated through nonclinical performance testing and labeling. And use error or improper device use, which can be mitigated through labeling. Please discuss whether the identified special controls for mammary sizers appropriately mitigate the identified risk to health and whether additional or different special controls are recommended.

The proposed special controls include the following. Number one. Nonclinical performance testing must demonstrate the mechanical function and durability of the device. Number two. The device must be demonstrated to be biocompatible. Number three. Performance data must demonstrate the sterility of the device. Number four. Performance data must support the shelf life of the device by demonstrating continued sterility and package integrity over the intended shelf life. Number five. Performance data must validate the cleaning and disinfection instructions for reusable devices. And number six. Labeling must bear all information required for the safe and effective use of the device, specifically including the following. One. A clear

description of the technological features of the device, including identification of device materials, shapes, and sizes. Two. Information on how the device operates. Three. Validated methods and instructions for reprocessing if the device is reusable, including the number of times the device can be re-sterilized. Four. A warning against implantation of the device. Five. A shelf life. And six. Disposal instructions.

Dr. Harris: Thank you. So, any comments from the panel regarding the appropriateness of these special controls to mitigate risk and assure reasonable safety of the sizers? Does anybody have any additional risks that they would like to see represented or feel should be represented in that list? Are any of those risks you feel unnecessary and shouldn't be included in the list of special controls? So, in summary, the lack of comment will lead us to believe that the committee is in agreement that these special controls do appropriately mitigate the risk associated with the mammary sizers?

Dr. Dean: Thank you. We appreciate your input.

Dr. Harris: Great. We'll move on to question number three if FDA will read that.

Ms. Ki: Question number three. Please discuss whether you agree with FDA's proposed classification of Class II with special controls for mammary sizers. If you do not agree with FDA's proposed classification, please provide your rationale for recommending a different classification.

Dr. Harris: So, by deductive reasoning, if we were satisfied with the special controls as outlined, and I think we are in agreement that these devices be classified as Class II. Does anyone disagree? Is that sufficient, Dr. Dean?

Dr. Dean: Thank you, we appreciate your input

Dr. Harris: I think that's the last of our questions. So we're now going to move into the Open Public Hearing portion of the meeting.

Public attendees are given an opportunity to address the panel to present data, information or views relevant to the meeting agenda. Ms. Nalls will read the open Public Hearing Disclosure process statement.

Ms. Nalls: Both the Food and Drug Administration, FDA believe in a transparent process for information gathering and decision making to ensure such transparency at the Open Public Hearing session of the advisory committee meeting, the FDA believes it's important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting.

For example, this financial information may include a company or group's payment of your travel, lodging or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue with financial relationships at the beginning of your statement, it does not preclude you from speaking.

Dr. Harris: Thank you, Ms. Nalls. FDA has received one request. The speaker will be given five minutes to speak. The open hearing speaker for this session is Dr. Diana Zuckerman.

Dr. Zuckerman: Thank you so much. I'm Dr. Diana Zuckerman, President of the

National Center for Health Research, we scrutinize the safety and effectiveness of medical products and we don't accept funding from companies that make those products, so I have no conflicts of interest.

Thanks for the opportunity to be here today. My expertise is based on postdoctoral training in epidemiology and public health. And my previous policy positions at Congressional Committees with oversight over the FDA, My previous position at the U.S. Department of Health and Human Services. And previous positions as researchers and faculty members at Harvard and Yale. So there are unique issues for the different types of wound dressings that you're considering today, but they do have some issues in common, and that's what I'm going to focus on.

Number one, they've been treated as 510(k) devices despite not being categorized as Class II or any other class. Number two, they've been used for years but FDA found very few studies pertaining to safety or effectiveness, and some of those studies were specific to particular types of surgery such as diabetic foot ulcer care. Number three, the information from FDA's adverse event reports on the MDR system is limited, but the FDA has identified several potentially serious adverse events including toxicity, infections, and delays in wound healing.

These are very important, obviously, because they can interfere with the success of surgery. And number four, most patients and surgeons assume that these products are proven to be safe and effective. They would be very surprised to know how little scientific evidence there is regarding safety and effectiveness.

This morning, you heard testimony from Madris Kinard from Device Events, and you saw her excellent analysis of adverse events based on information from the FDA database.

At our request, she also provided an analysis to us of wound dressings for our research center to look at, and her analysis was based on FDA total product lifecycle database. The results indicated thousands of reports of contamination and problems with nonsterile packaging of wound devices. Most were from the last four years. For the animal derived wound dressings, which are collagen dressings, there are 126 MDRs, but also 12 recalls. So FDA and other experts agree that MDRs are underreported.

It's a voluntary system, and as panel members mentioned this morning, it's difficult to distinguish between adverse caused by the device and those caused by the procedure. And we all know that surgeons are very busy and not always – and they don't necessarily have an incentive to report adverse events if the causes are unclear.

Keep in mind, for example, if a patient's wound becomes infected, surgeons would not necessarily report it as an MDR for the wound dressing. So the FDA has delineated very clear special controls for these devices if they are considered Class II and continue to be cleared through the 510(k) process.

These are very good efforts that would improve upon the current regulatory policies for these devices, but they do have two major short comings. Number one, they don't include inspections. And those are the process inspections would be the way to reduce problems with contamination or nonsterile packaging. And number two, none of these controls will provide scientific data on the safety and effectiveness of any of these wound dressing products and that's the one crucial type of information that's missing.

Insufficient information is currently available, especially regarding which specific products are safest and most effective for which indications. The issue isn't just different types of

wound dressings, but the products made by different companies because it's likely that of course some are better than others. And that's why I encourage you to urge the FDA to categorize wound dressings as Class III so that we will finally have well designed clinical trials to determine safety and effectiveness.

One more thing. What about registries? Registries can collect important information, but as you consider all the medical devices being discussed today and tomorrow, please remember that registries are controlled by medical societies and as such, the data from them are not available to the public or the FDA except for the information that those medical societies choose to make public.

Unfortunately, we can't rely on registries to provide objective, comprehensive information about safety and effectiveness. Thanks very much for the opportunity to speak today. And I'd be happy to answer any questions.

Dr. Harris: Thank you, Dr. Zuckerman. So, do we have any clarifying questions from the panel for Dr. Zuckerman? Not hearing any questions, we'll now invite the FDA to start their presentation. I would like to remind the public observers at this meeting that while the meeting is open for public observation, public attendees may not participate except at the specific request of the panel chair. FDA, you may now begin your presentation.

Dr. Lamichhane: Good afternoon. My name is Tek Lamichhane and I'm a lead reviewer in the division of Infection Control and Plastic Surgery devices within the Office of Surgical and Infection Control Devices in CDRH Office of Product Evaluation and Quality. Today I will be presenting information regarding our effort to classify wound dressings with animal-derived materials regulated under product code KGN.

These devices are currently unclassified and we are looking for your thoughts and recommendations on the appropriate regulatory classification for these devices. This is the outline for my presentation. These are the items that we will be discussing today. Wound dressings with animal derived materials are intended to cover and protect the wound, absorb exudate, and maintain appropriate moisture balance within the wound.

The dressing is made up entirely or in part of decellularized extracellular matrix, collagen, gelatin or keratin. The source animal can vary and include different mammals, birds, amphibians or fish. Similarly, they can be derived from different parts of the body. The dressings may be manufactured with other non-animal derived materials as well.

They are available in different forms such as a sheet, pad, gel, or powder. The animal derived materials in the wound dressing support the intended use of the dressing to cover and protect the wound, observe, exudate, and maintain appropriate moisture balance within the wound. The animal derived materials may also support the physical integrity of the dressing. We want to emphasize that the animal derived materials are not intended for biological actions related to wound healing, such as to accelerate wound dealing. Also, wound dressings with animal derived materials that are part of this classification do not contain any antimicrobials, drugs, or biologics.

The indications for use or IFU statement identifies the disease or condition that device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended. These devices have been cleared with both prescription and over the counter use indication. For prescription use, a broad range of wound types are included, ranging from partial and full thickness wounds to radiation dermatitis. For over the counter use

devices they are mainly indicated for the management of minor wound types such as minor cuts, minor scraps, minor burns, and minor lacerations. These wound dressing have also been cleared to maintain a moist wound environment and provide a full recovering for meshed autograft. Wound dressings with animal derived materials are a preamendment unclassified device type.

This means that this device type was marketed prior to Medical Device Amendment Act of 1976. It was not classified by the original classification panels. Currently, these devices are being regulated through the 510(k) pathway and are clear for marketing if their intended use and technological characteristics are substantially equivalent to a legally marketed predicate device.

Since these devices are unclassified, there is no regulation associated with the KGN product code. To date, more than 120 devices have been cleared through a pre-market notification 510(k) pathway under the product code KGN. Please refer to section two of the executive summary for a complete list of cleared devices under Protocol KGN.

On November 17th, 1998, the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee made to discuss the classification of porcine wounds dressings cleared under protocol KGN among other unclassified pre amendment devices. The panel voted unanimously to recommend that Agency classify porcine would dressing as Class I medical devices, although a majority of panelists agree that these products should not be exempted from 510(k) pre-market notification due to risks associated with material sourcing and viral transmission.

Since 1998, there have been significant developments including new technologies and indications for use, and more recent products clear under the product code KGN have been composed of materials from many different sources and are indicated from broader ranges of

wounds. In addition, FDA's understanding and experiences with animal derived materials have further developed since 1998 panel meeting. Therefore, FDA's convening this classification panel to discuss the current landscape of product technology, indications of use, safety, and effectiveness, and risks to health on which to base classification of wound testing with animal derived materials.

Wound dressings with animal derived materials are used to cover and protect the wound to absorb exudate and to maintain appropriate moisture balance within the wound for a variety of acute and chronic wounds. Acute wounds such as cuts, post-surgical wounds are more predictable and heal at expected rate. However, chronic wounds such as ulcers are unpredictable and heal at unexpected rate.

The pathophysiology of the wounds also varies greatly. Alternative treatment options include a range of standard of care methods that depend on the wound characteristics. Wounds can be managed with other wound dressings that may cover and protect the wound and provide a moist wound environment or with compressive dressings, bioengineered dressings, wound dressings containing antimicrobials or other modalities including negative pressure wound therapy devices, pressure relief devices, hyperbaric oxygen and topical drugs.

Generally standard of care treatment for wound care includes wound debridement, rinsing, and providing a most wound environment. We conducted a literature review to identify any published information between April 1st, 2012 and July 18th, 2022 regarding the safety and effectiveness of wound dressings with animal derived materials.

Sources were limited to publication in English and excluded conference proceedings and abstract. A total of five studies were determined to be relevant to the safety and or effectiveness

of wound dressings with animal direct materials. Of the five studies, two were randomized control trial or RCTs, while the remaining three studies used a retrospective design.

I will briefly summarize some of the main take home points from each of the review article in the next few slides. In terms of safety, two of the five articles reported adverse events associated with the use of wound dressing with animal derived materials. Both the studies reported mild unspecified local adverse reactions. One study found no difference in adverse events between standard of care associate treatment, which consisted of sharp debridement, infection, elimination, use of dressing and uploading and wound dressing with animal derived material. None of the five studies reported systemic adverse tissue reactions.

In terms of effectiveness, the source identified five studies of wounding dressing with animal derived materials, which reported healing time. The first study showed no difference in wound closer time between standard of care and wound dressing with animal derived materials.

In the second and third study, they compared wound dressings with animal derived materials with a bioengineered cellular product BLLC, which is intended to accelerate the wound healing. Even though BLLC was found more effective than wound dressings with animal derived materials, they are still effective at supporting wound healing.

The fourth study compared the use of collagen with oxidized regenerated cellulose, ORC which is a dressing that contains both collagen and silver. While the data favors the ORC product, the wound dressing with animal derived material is still supported wound healing.

In the fifth study, they compare wound healing time between collagen and gelatin, which are both animal derived wound dressings and found that the healing time is comparable. Overall wound dressings with animal derive materials were shown to be effective at supporting wound

healing, even though they may have slower wound closer rates than bioengineered skin substitutes, which is expected.

Adverse event associated with wound dressings with animal derived materials is reported in these studies were mild and limited to local reactions. None of those studies reported any systemic adverse reactions. On the whole, the extent of the evidence base for the literacy review is low given only 5 studies met the inclusion criteria and the high potential for bias in retrospective study designs and in studies funded by device manufacturers.

The next three slides provide background information for medical device reports or MDRs. The MDR system provides FDA with information on medical device performance from patients, healthcare professionals, consumers, and mandatory reporters, manufacturers, importers, and device user facilities. FDA receives medical device reports of suspected device associated deaths, serious injuries and malfunctions.

The FDA uses MDR to monitor device performance, detect potential device related safety issues, and contribute to benefit risk assessment of these products. MDRs can be used effectively to establish a qualitative snapshot of adverse, events for a specific device or device type detect actual or potential device problems used in real world setting or environment, including rare, serious or unexpected adverse events. Adverse events that occur during long term device use, adverse events associated with vulnerable populations, off-label use error.

Although MDRs are a valuable source of information, this passive surveillance system has limitations including the potential submission of incomplete inaccurate, untimely unverified, duplicated or biased data.

In addition, the incidents or prevalence of even cannot be determined from this reporting

system alone due to potential under-reporting of events and lack of information about frequency of device use. Finally, the existence of adverse event report doesn't definitely establish a causal link between the device in the reported event.

Because of this limitation, MDRs comprise one of the FDA tools for assessing device performance, as such MDR numbers and data should be taken in the context of other available scientific information. We searched the manufacturer and user facility device experience aka MAUDE database to identify a adverse event related to the user wound dressing with animal-derived materials, product code KGN entered between April 1st, 1988 and April 1st, 2022. Our source identified total of 119 reports, of those 103 met the criteria of serious injury and 16 where related to malfunction of the device. 72 were reported from the U.S. and 47 didn't have information on the reporting country.

Manufacturers submitted 112 reports and the remaining seven reports were voluntary submission. This table shows the types of adverse event reported in the MDRs for wound dressing with animal derived materials. The most frequently reported adverse events were unspecified infection, swelling, and bacterial infection.

The MDR events observed are expected for this device type and consistent with the risks found in the literature. These slides provide background information for recalls and medical device recall database. The medical device recall database contains medical device recalls classified since November 2002.

Since January, 2017 it may also include correction or removal actions initiated by a firm prior to review by the FDA. The status is updated if the FDA identifies a violation and classify the action as a recall and again when the recall is terminated. FDA recall classification may occur

after the firm recalling the medical device product conducts and communicates with its customers about the recall.

Additional information on the recall history of wound dressings with animal derived materials will be presented in the next slide. The medical device recall database was reviewed for product code KGN as of August 18th, 2022 and we identified eight Class II recalls. The definition of Class II recall can be pound on page 14 of the wound dressings with animal derived materials executive summary.

The recalls were related to power seal failure, inadequate sterilization, failure of sterility testing, acceptance criteria issued in device labeling and visual appearance. These recalls are related to manufacturing errors and they do not suggest any additional risks related to the wound dressings with animal derived materials as a product class. To determine the appropriate classification for wound dressings with animal derive materials, we have identified risks associated with these devices and possible mitigation for these risks. We'll be asking the panel for input on the list of risks and mitigation. In evaluating the risk to health associated with the use of wound dressings with animal derived materials we considered information from the adverse event reported in FDA's MAUDE database, the published scientific literature, device recall history, and FDA's experience with these devices.

Here are the five risks to health identified for wound dressings with animal derived materials. Adverse tissue reaction, this can result from the use of device materials that are not biocompatible for devices intended to degrade in the wound. Delayed tissue response or toxicity can result from the degradant, such as crosslinking agents used to crosslink the animal derive materials. Infection. This can result from inadequate device sterilization, inadequate viral

inactivation or inadequate packaging integrity. Immunological reaction, this can result from a device derived from a new animal source or protein denaturization/modification due to the manufacturing conditions. Transmission of pathogens and parasites. This can result from contaminated animal sources, feed, inadequate processing and viral inactivation of the animal derived materials. Delays in wound healing. this can result from the use of device materials, which may interfere with the wound healing process

We believe general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness and sufficient information exists to establish special controls to adequately mitigate the risks to health and provide reasonable assurance of the device safety and effectiveness for this device type.

Here is a table with the identified risks to health and proposed mitigation measures which we propose to be addressed through special controls. To mitigate the risk of adverse tissue reaction, we recommend biocompatibility evaluation, pyrogenicity testing, performance testing and descriptive information. To mitigate the risk of infection, we recommend sterilization testing/validation information, shelf-life validation, labeling, and risk management assessment of animal derived materials. To mitigate the risk of immunological reaction, we recommend performance testing, material characterization, risk management assessment of animal derived materials and labeling. To mitigate the risk of transmission of pathogens and parasites, we recommend risk management assessment of animal derived materials, performing testing and labeling. To mitigate the risk of delays in wound dealing, we recommend performance testing and descriptive information biocompatibility evaluation and labeling.

Here is our proposed classification regulation for wound testing with animal derived

materials. Part a of the regulation defines the device is follows, a wound dressing with animal derived materials consists either entirely or in part of materials such as collogen, gelatin sourced from an animal and is intended to cover and protect a wound to absorb exudate and to maintain appropriate moisture balance within the wound. Such wound dressing may be manufactured with other natural or synthetic materials to achieve the final physical state of the dressing, including sheet, gel, powder. The animal derived materials incorporated in these wound dressings are intended to provide or support the physical structure of the dressing and are not intended for biological actions related to wound healing for example, to accelerate wound healing. A wound dressing with animal derived material doesn't contain any antimicrobials, drugs or biologics.

Furthermore, we are proposing these devices be classified as Class II devices with special controls. Based on the identified risks in recommended mitigation measures FDA believes that the following special controls on this slide and the next two slides will provide reasonable assurance of the safety and effectiveness for wound dressings with animal derived materials under protocol KGN.

Number one, performing testing and descriptive information must demonstrate the functionality of the device to achieve the specified use, including establishing the physical and chemical characteristics of the device. The following must be provided, identity, quantification, and purpose of each component in the finished product. Specification and characterization of each component in the finished product and final release is specification for the finished product.

Number two, performance data must demonstrate the sterility of the device.

Number three, the device, including any degradants, must be demonstrated to be biocompatible, non pyrogenic and contain endotoxin level within acceptable limits.

Number four, performance data must support the cell type of the device by demonstrating continued sterility, package integrity and device functionality over the identified shelf life.

Number five, performing data must demonstrate that the device performs as intended under anticipated condition of use, including device degradation, if applicable and evaluation of expected worst-case conditions.

Number six, if the device contains materials derived from a new animal species or from manufacturing processes which cause structural changes that is denaturation or modification to the animal protein performance data, for example, patch and prick-testing, human repeat insult patch testing must demonstrate that device is not immunogenic.

Number seven, the following information must be provided to support the safety of the animal derived materials.

Number one, documentation of the processing methods including animal species, origin, husbandry, and tissue selection, as well as methods for tissue storage, transport and quarantine that mitigate the risk of parasites and pathogens.

Number two, performance data, which demonstrates adequate removal that is clearance, or inactivation of parasites and pathogens, including bacteria, mycoplasma, fungi, viruses, and other transmissible spongiform encephalopathy agents from the final finished device.

A risk management assessment for the improves of animal derived materials, which considers any probable risk associated with the presence of animal tissue in the final finished wound dressing, including pathogen and parasite infection and immunological reaction. The risk management assessment must describe how these risks are controlled and mitigated by the method of animal husbandry, tissue selection, tissue handling, manufacturing, and process

controls data documenting the ability of the manufacturing and sterilization to ensure adequate removal that is clearance or inactivation of parasites and pathogens from the final finished device.

Number eight, the labeling must include a description of intended user population. Number two, specific instruction regarding the proper placement, sizing, duration of use, frequency of dressing change, maximum use life per application of the dressing, maximum total use life of the dressing and removal of the dressing, if applicable.

Number three, a list of each ingredient or component within the finished device, including the functional role of that ingredient or component within the device.

Number four, if the device is non-reabsorbable, a warning statement for the potential retention of material in the wound or the surrounding area.

Number five, a contraindication for any known sensitivity to components within the device.

Six, a contraindication if there are incompatibilities with other therapies.

Number seven, shelf life.

Number eight, A statement regarding when to discontinue use of the device after multiple reapplication based on biocompatibility and performance testing if applicable.

Number nine, for devices indicated for over-the-counter use, the indications must specify conditions, uses, or purposes for which the product may be safely administered by a lay user without the supervision of a licensed medical practitioner.

Number ten, any statement in the labeling must be clear such that they may be understood

by the end user, supported by appropriate evidence and consistent with the intended use of covering and protecting a wound, absorbing exudate, and maintaining appropriate moisture balance within the wound. Number 11, disposal instruction.

This concludes our presentation. Thank you for your time and attention.

Dr. Harris: Thank you. Does the panel have any brief classifying questions of the presenter regarding the content of that presentation? Dr. Li.

Dr. Li: Maybe you could clarify a little bit, is there a limitation or definition by what you mean by animal derived materials? It seems like without some definition that could include a very wide variety of things from anything from fish skin to growth factor. So does the FDA have in mind the limitation to what animal derived material means?

Dr. Dean: I'm going to get back to you on that. As you noted, it can mean a number of things and from a number of animals. But I will clarify that.

Dr. Li: It would seem like it would make a difference if you're talking about collagen or I read papers where they're using the fish skin from Nile tilapia for wound dressing.

Or if you're going to pick some growth factor or some protein, it would make a difference of my concern.

Dr. Dean: We have to remove growth factors. Remember the purpose of these devices are really for simply covering the wound and supporting the natural wound healing process by protecting it, they provide a moist wound environment and absorb any exudate.

So that's it.

Nothing that would affect wound healing and make no claims regarding wound healing.

Dr. Li: So if somebody is going to take some synthetic material and add something to it to promote wound healing, this would not be included in what we're talking about?

Dr. Dean: This would not be included.

Dr. Li: Okay. Thank you.

Dr. Harris: Any other questions? No other clarifying questions regarding the presentation, then I would like to move on to a deliberation of the FDA's questions for the panel.

And once again, I'll remind everyone as you've been doing very well, to identify yourself when you make comments and make sure your microphone is unmuted.

So if we could please have the first question from FDA.

FDA: We have the following questions for the panel. We are looking for thoughts and recommendations on the appropriate regulatory classification for these devices.

Question number one, FDA has identified the following risks to health for wound dressings with animal derived materials, adverse tissue reaction, infection, transmission of pathogens and parasites and delays in wound healing.

Please comment on whether you agree with inclusion of all the risks in the overall risk assessment of wound dressings with animal derived materials under product code KGN.

In addition, please comment on whether you believe that any additional risks should be included in the overall risk assessment of these wound dressings with animal derived materials.

Dr. Harris: Any questions or comments from the panel? Dr. Diegelmann.

Dr. Diegelmann: Just concerned about the risks involving exasperated formation of

keloids or hypertrophic scars with the use if this. Should that be put into a warning for the users.

Dr. Harris: You're wondering whether these dressings could promote hypertrophic scarring?

Dr. Diegelmann: Correct. Should patients that have a history of keloid formation be informed that this may cause additional keloids. Maybe the plastic surgeons can weigh in on that

Dr. Harris: Does anyone on the panel have information regarding evidence that hypertrophic scarring in patients at risk for that skin condition?

Dr. DeLong: I haven't seen any data

Dr. Harris: This is Dr. DeLong talking.

Dr. DeLong: Sorry, apologies. This is Dr. DeLong. I haven't seen any data to support that, although I'm not saying it can't happen. I just never –

Dr. Harris: Dr. Hunt?

Dr. Hunt: Yes. Hi, Kelly Hunt. I would say a lot of times when these wound dressings are utilized, it's because there's already issues related to wound healing. And so you might anticipate that there would be a higher rate of hypertrophic scars or issues related to that, not necessarily caused by the device but related to the patient's underlying wound healing. Thank you.

Dr. Harris: Thank you. So are there any other risks that the panel feels should be included in any proposed special controls for these wound dressings? Ms. Block?

Ms. Block: A good point was made as what species these are derived from. And maybe one thing as far as the risk is defining the species used. I know it says animal derived

materials. But it doesn't say specifically to define which animal is used for the materials. So, perhaps, maybe listing a risk of the different species out there, if I'm saying that correctly. I apologize if I'm being not clear.

Dr. Harris: So are you suggesting that perhaps there would be information regarding the relative risk of a reaction to something from a cow versus something from a fish versus something from a pig?

Ms. Block: Correct.

Dr. Harris: So it sounds like the suggestion is there be some quantification associated with the a likelihood of a patients reacting so a specific animal derived product and linking that to the specific species. Any other thoughts or comments? Ms. Fisher.

Ms. Fisher: I just wondered if there's any thoughts or considerations given to notify or informing the patient ahead of time as to what species of animal might be involved in this. I'm just thinking ahead of like if it's a porcine product, if there are any cultural or religious issues that might come up for a certain sector of the population.

Dr. Dean: If I could, you're actually getting ahead of us a little bit as to the special controls in the next question. So I'll redirect the panel to the question. This concerns the risks that you see associated with these devices.

Dr. Harris: I think we'll get to your question, Ms. Fisher, in just a minute. Ms. Agazie. You're still muted.

Ms. Agazie: What about the retention of dressing material in the wound as a risk factor?

Dr. Harris: So I thought that was listed, but perhaps I was mistaken. Can FDA clarify was there a risk listed in terms of retention of nonabsorbable components of the wound dressing? Is our presenter Dr. Lamichhane.

Dr. Dean: I'm taking a look at that slide. The risk, just to clarify adverse tissue reaction, and I believe that part of this does have to do with the degradation of the device in the wound, infection, immunological reaction, transmission of pathogens and parasites and delays in wound healing. Those were the listed risks.

Dr. Harris: So it doesn't specifically risk retained wound dressing components?

Dr. Dean: Not specifically.

Ms. Agazie: So can the be included as a risk factor?

Dr. Harris: Yeah, that's a suggestion. Dr. Li? You're muted, Dr. Li.

Dr. Li: Sorry. Steve Li. I thought I would repeat my question, because maybe I was not as clear as I wanted to be, I'm a little bit nervous about the lack of the definition for animal derived materials without a definition. Because it seems to be as a materials person, there's lots of different animals. And for each animal, there's lots of materials that I could extract from them in part or in whole. And if the challenge is could I find some animal in some derived part that wouldn't work in a wound, I could probably do that. So I'm a little uncomfortable with the general lack of description.

I don't know if anybody else is, of what animal derived materials means.

Dr. Dean: I would point out, we do have a guidance document on animal derived materials for medical devices. And I believe that this has been left broad, but there are as you

heard recommended special controls that would potentially mitigate any risks you might see in any of these potential materials.

Dr. Harris: Dr. DeLong?

Dr. DeLong: I guess to build on Dr. Li's question, a common strategy for manufacturers is to take a particular component and add it. I know you have in the identification that they can't make specifically marketing claims related to biological activity, does that mean that you would specifically exclude products that have biological activity, for example, in the FRO classification, manufacturers are not allowed to say that it has antimicrobials, but a lot of those products have antimicrobial drugs and they say it's added as a preservative.

Will the FDA be making a distinction here where if it has the potential to biological activity is it kicked out of whatever this is, KGN, versus as long as they don't make a specific claim, it gets to stay in KGN?

Dr. Dean: I believe so. And we're taking your advice here as well. So if that is something that you wanted to make sure that we include, please state that and we'll include that in our advice.

Dr. DeLong: Thank you.

Dr. Harris: Any other comments regarding the list of risks that have been identified for these wound dressings containing animal derived products? If not, then, Dr. Dean, I believe that the committee with the comments that have been made, are satisfied with the risk as listed though I assume some of the discussion will continue with the deliberation over the special controls themselves.

Dr. Dean: Agreed. This is sufficient for our discussion on risks. And I look forward to our upcoming continued discussion on the special controls.

Dr. Harris: Great. Next question. FDA, if you will reads the next question for the panel.

FDA: Question number two. Section 513 of Food, Drug and Cosmetic Act states a device should be Class III if insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of its safety and effectiveness and the device is purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury.

A device should be Class II if general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness and there is sufficient information to establish special controls to provide such assurance.

A device should be Class I if general controls are sufficient to provide reasonable assurance of the safety and effectiveness or insufficient information exists to determine that general controls are sufficient to provide reasonable assurance of the safety and effectiveness or establish special controls to provide such assurance. But is not purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing the impairment of human health and does not present a potential unreasonable risk of illness or injury.

FDA believes general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness and sufficient information exists to establish special

controls to adequately to adequately mitigate the risks to health and provide reasonable assurance of the device safety, and effectiveness for this device type. As such, FDA believes that class II is the appropriate classification for wound dressings with animal derived materials cleared under product code KGN.

The following risk mitigation table which outlines the identified risks to health for this device type and the recommended controls to mitigate the identified risks.

This was the identified risks and mitigation as shown earlier. To mitigate the risk of animal tissue reaction, we recommend biocompatibility evaluation, pyrogenicity testing, performance testing and descriptive information, risk management assessment for animal derived materials and labelling. To mitigate the risk of infection, we recommend sterilization testing, validation information, shelf life validation, labeling and risk management assessment of animal derived materials. To mitigate the risk of immunological reactions, we recommend performance testing, material characterization, risk management assessment for animal derived materials, and labeling. To mitigate the risk of transmission of pathogens and parasites, we recommend risk management assessment of animal derived materials, performance testing, and labeling. To mitigate the risk of delays in wound healing, we recommend performance testing and descriptive information, biocompatibility evaluation, and labeling.

Please discuss whether the identified special controls for wound testing with animal derived materials appropriately mitigate the identified risks to health and whether additional or different special controls are recommended.

Number one, performance testing and descriptive information must demonstrate the functionality of the device to achieve the specified use, including establishing the physical and

chemical characteristics of the device. The following must be provided: Identity, quantification and purpose of each component in the finished product. Specification and characterization of each component in the finished product. And final release specifications for the finished product.

Number two, performance data must demonstrate the sterility of the device.

Number three, the device including any degradants must be demonstrated to be biocompatible, nonpyrogenic, and contain endotoxin level within acceptable limits.

Number four, performance data must support the shelf life of the device by demonstrating continued sterility, package integrity, and device functionality over the identified shelf life.

Number five, performance data must demonstrate that the device performance as intended under condition of use including device degradation if applicable, and evaluation of expected worst case conditions.

Number six, if the device contains materials derived from a new animal species or from manufacturing processes which cause structural changes that is denaturation, modification to the animal protein, performance data, for example, patch and prick testing, human repeat insult patch testing must demonstrate that the device is not immunogenic.

Number seven, the following information must be provided to support the safety of the animal derived materials. Documentation of the processing methods, including animal species, origin, husbandry, and tissue selection as well as methods for tissue storage, transport, and quarantine that mitigate the risk of parasites and pathogens.

Number two, performance data which demonstrates adequate removal that is clearance or inactivation of parasites and pathogens including bacteria, mycoplasma, fungi, viruses and all

other transmissible spongiform encephalopathy agents from the final finished device

Number three, a risk management assessment for the inclusion of animal derived materials which considers any probable risk associated with the presence of the animal tissues in the final finished wound dressing including pathogen, parasite infection and immunological reaction. The risk management assessment must describe how these risks are controlled and mitigated by method of animal husbandry, tissue selection, and tissue handling, manufacturing and process controls C data documenting the ability of the manufacturing and sterilization procedure to ensure adequate removal, clearance or inactivation of parasites and pathogens from the final finished device.

Number eight, labelling must include a description of the intended user population. Number two, specific instructions regarding the proper placement, sizing, duration of use, frequency of dressing change, maximum use life per application of the dressing, maximum total use life of the dressing, and removal of the dressing if applicable.

Number three, a list of each ingredient or component within the finished device, including the functional role of that ingredient or component within the device.

Number four, if the device is non reabsorbable, a warning statement for the potential retention of material in the wound or the surrounding area.

Number five, a contraindication of any known sensitivity to components within the device.

Number six, a contraindication if there are incapabilities with other therapies.

Seven, shelf life.

Eight, a statement regarding which to discontinue use of the device after multiple reapplication based on biocompatibility and performance testing, if applicable.

Number nine, for devices indicated for over the counter use, the indications must specify conditions, uses or purposes for which the product may be safely administered by a lay user without the supervision of a licensed medical practitioner.

Number ten, any statements in the labelling must be clear so that they may be understood by the end user, supported by appropriate evidence, and consistent with the intended use of covering and protecting a wound absorbing exudate, and maintaining appropriate moisture balance within the wound.

Number 11, disposal instructions.

Dr. Harris: Thank you for that. So now, I'd like to hear from the panel with comments regarding thoughts on the special controls. But we'll first hear a comment from Dr. Dean.

Dr. Dean: Thank you. I do have a clarification that I think will may be get to Dr. Li's earlier concern about the variety of animal sources. So the manufacturing processes for animal derived materials is very stringent. The chemical treatments and the final sterilization. It eliminates any cellular components including nucleic acids, growth factors and more. And these manufacturing processes need to be validated for this as well as the viral inactivation. So, keep in mind that the intended use of these devices is simply to cover the wound, provide that moist environment.

Dr. Harris: Thank you. Any comments from the panel? I have a few comments. And I guess I'd like to preface my comments by saying that I am my comments are somewhat informed, certainly influenced by the interaction with companies producing these products and

marketing them to practitioners and patients.

Secondly, I'm struck as I'm sure we all are that with 120 cleared products on the market, there is a striking scarcity of data. And the data itself that is available is of quite poor quality either uncontrolled or poorly controlled. So really getting to a question or a statement raised earlier by our public speaker, Dr. Zuckerman, it seems to me that there is really no data demonstrating that these dressings are actually effective. And I see it seems to me there's a lot of steps being taken to make sure they're safe, which of course is important. But I wonder whether we're de-emphasizing effectiveness in this review.

And it seems to me that many of these special controls, you really cannot derive the information in the absence of clinical testing. I don't understand how you'll be able to determine whether a dressing delays wound healing in patients without testing it in patients. I won't be it’s a little hard for me to determine how you would determine how frequently the dressing should be changed, what's the maximum use or what point should discontinue use of these dressings without testing them in humans?

So, I guess my question to the panel and my comment is do these special controls provide the opportunity for requiring manufacturers to actually demonstrate effectiveness of the dressing relative to a specified standard of care control to demonstrate that they should be, in fact, utilized?

And my last comment, I know there's a lot there to unpack, but this other requirement of the special controls that we demonstrate the purpose of each component of the dressing. When you look at these dressings, it's hard to envision what people had in mind when deciding to include one component or another. Fish skin comes to mind pretty quickly. So I'd just like to hear

maybe some comments from FDA or other panel members regarding any of those topics that I've touched upon.

So Dr. Dean, quick question to you. Do the special controls allow for a requirement for clinical testing or does that automatically elevate the product classification to Class III?

Dr. Dean: That would not automatically change the classification. You can recommend that clinical testing be among the special controls.

Dr. Harris: All righty. Dr. DeLong?

Dr. DeLong: Thank you, Dr. Harris. Those are excellent points. I guess I can give my opinions in response to them.

I agree that there does seem to be a significant paucity of clinical data, a lot of products, not many studies. In terms of the identification of the products themselves, the FDA displayed, it does seem that effectiveness in terms of wound healing was specifically mentioned as, you know, these products are not designed to accelerate wound healing. So that is called out that when we look at effectiveness, that is not the effectiveness metric, per se, in the way that these products are regulated. In terms of measuring wound healing effectiveness. Particularly with clinical data, I remember when I worked at the FDA the was an ongoing controversial topic because it's hard to know what an effectiveness outcome is. Time until full wound healing is often thrown out there, but if a patient has bad vascular disease or a diabetic wound they may never heal that wound and no animal product is going to heal it. So trying to put it into patients and figure out which one is going to make the wounds heal faster, which isn't even a piece of the product code identification is often not feasible.

And so, I think a lot of the performance there's a special control for performance testing,

I suspect, that would be done largely in animal preclinical data where they're well defined models where you can more rigorously test products against each other, against, you know, a placebo control where we know that the animal will heal and things like that. And then, I think there was another point but now I'm blanking.

I guess as I'm thinking about these products, there's another similar type of product that's animal derived that we put in patients, and those are surgical mesh devices. With the exception of use in breasts, these are all Class II devices where we surgically implant them. We don't ever intend to take these devices out and they are mitigated entirely by special controls and considered Class II without a requirement for clinical data for each product. So in light of that regulation, it's hard for me to see topically applied animal products which are removed as being any higher than Class II.

Dr. Harris: Thank you. Dr. Diegelmann.

Dr. Diegelmann: I'm looking at page 7 of executive summary, and it states that wound dressings with animal derived materials not been cleared for indication such as wound treatment, promotion or acceleration of wound healing. Such indications may pose a different intended use than the cleared indications and are outside of the scope for this panel meeting. Does that answer your question or address your question?

Dr. Harris: Actually, no. I hear what you're saying and I appreciate your comment and Dr. DeLong's. My thinking is how are you going to demonstrate that the dressing maintains a moist wound environment? What is actually moisture balance and how is that going to be measured? And how do you determine as I was saying earlier, the question of the frequency, and at what point do you discontinue, let along the fact that they’re actually, even amongst the scarce

data that is there, there is demonstration of one wound product that did in fact delay wound healing, something I don't think you can determine in cell culture or in an animal. Those are the sorts of things I'm not suggesting these products need to accelerate or be products marketed to enhancing wound healing, though the reality is that is frequently what you're told by the sales representatives of the companies who are marketing these products, but that's not FDA's problem. That's just someone crossing the line, perhaps, in terms of their indication for use. But I'm just saying in terms of just the basic performance characteristics, not the wound healing characteristics of these dressings, how are you going to determine that without actually using it in patients. Dr. Galandiuk.

Dr. Galandiuk: I agree with you Dr. Harris, FDA has always been safety and efficacy. And here I totally agree with you. There's loads of these devices on the market. And patients pay a huge amount for these things. I mean, these are very expensive products in many cases. And the consumer, I think, has a right to demand that there's some demonstration of efficacy. And I very much support your concerns.

Dr. Harris: Dr. McGrath.

Dr. McGrath: I'm just wondering, to help answer your question, I agree that there's a plethora of these things. The presentation the FDA mentioned there are a 120 of these devices that already have gone through the process. If you look under the special controls, the first one is performance testing to demonstrate functionality. Maybe it would help us if we knew what that meant. So what does that mean to the FDA or Dr. DeLong, when you said it, you implied that involved animal testing. So I guess I'm asking the FDA, is that what performance testing to show functionality, is that consistently done, and what does that mean? What does that mean? What

does that involve?

Dr. Harris: Dr. Dean or Dr. Lamichhane.

Dr. Dean: Yes, I think I would like to ask our subject matter expert to give you a little bit more about the testing that we do see.

Dr. Lamichhane: This is Dr. Lamichhane I'm the subject matter expert in this product. Yeah. So in terms of the testing, when we receive the product we do – yeah, some of the animal study like for example wound healing study we compare that we don't see any toxicity effect, for example, system toxicity and others. Some of the testing that we do, the vitral inactivation just to make sure that they are, you know, not pathogenic and didn't contain any pathogens or any agents from the animal sources from whatever they were indicated. And yeah, the performance testing, some of the, let's say, absorbency since they are indicative for the absorbing would exudate, so they also do moisture like the absorbency testing and so on. Yeah, does it answer your question?

Dr. Harris: So, I mean, I think the animal testing, I'm assuming this predominantly in rodents?

Dr. Lamichhane: They do also in pigs.

Dr. Harris: My thinking from a clinical point of view is the animal testing is good to exclude obvious toxicity, but the absence of toxicity, or say for example the absence of delayed wound healing in a pig would not exclude it in a diabetic human. And so, I think that it's safe to maybe go in a step wise fashion but it would seem that you would want to end up with humans.

One other comment. Dr. DeLong brought up a good point that all of these mesh

prosthetics, an actual area I know more about than wound dressings, I certainly hope in the future we'll have a similar discussion about those products as well that are being implanted and where there's now a clear evidence of lack of efficacy of many of these combination products, that are actually frankly dangerous because they are permanent implants. Dr. Dean.

Dr. Dean: I just wanted to remind you that, you know, should this panel agree in the next question that this would be a Class II device, that the idea is that the special controls would assure us of the safe and effective use of these devices and substantial equivalence to those that are already on the market. It can be a little bit difficult if we're adding suddenly additional clinical testing to this, though, we will take your advice, anything that you think would be important in these special controls. But remember we want to understand what risks are you mitigating here?

Dr. Harris: Miss Block?

Ms. Block: Dr. Dean, I have a question for you, just so I fully understand. Based on these special controls, I feel Class II will limit contamination and provide a description and provide quality control of these products. That is without a doubt. You said that we can add, or suggest that you add clinical testing as one of the special controls. Can you define that a little bit more? Does that then put it into a Class III? Or how does that work?

Dr. Dean: No, it does not change the class. The special controls are those that you feel are important to ensure that these devices are safe and effective and substantially equivalent to those that are on the market.

Ms. Block: So if we're looking for efficacy, something we should add is the clinical testing to the special controls and keep it as a Class II.

Dr. Dean: Remember, then, that this would be required of all future 510(k)s in this product code. So, even if the first devices come in with those clinical trials, and it means that everyone even ten years from now are also required to do the same. That's part of the special controls. They all have to meet those special controls.

Dr. Harris: But you say that. Is our panel charged with trying to figure out what's most convenient for getting new products on the market or what would be in the best interests?

Dr. Dean: What is important in establishing the safety of these devices.

Dr. Harris: Safety and effectiveness, correct?

Dr. Dean: Safety and effectiveness. Although, again, remember that special controls are then required for all devices of this type to go on the market. So if what you are looking for – sounds like you're interested in a study that demonstrates the effectiveness of these devices. If you add this to the special controls, they will then be required again and again.

Dr. Harris: Right. That's what I'm saying is that if the dressing is there to protect the wound, to absorb exudate, and to maintain moisture balance, demonstrating that it does that in a human wound would seem to me relatively straightforward. And if that were a requirement for future dressings that we're making the same exclamation, that would seem also logical to me. Dr. DeLong.

Dr. DeLong: I guess I just wanted to give my opinion on the topic that you guys are discussion in terms of, correct me if I'm wrong, the way this I don't proceed is if you don't include clinical trial data necessarily and special controls, but if there's a significantly different component of a wound dressing, you can say that's a new questions of safety and effectiveness and could that manufacturer require clinical trial data to demonstrate safety and effectiveness and

following products that use the same components with then be cleared through a 510(k) pathway, I meant that is the purpose of the 510(k) pathway, is that every manufacturer coming in with a mechanical device with very similar components, doesn't have to go out and enroll a hundred new patients to demonstrate that it performs same as the prior product. So it could follow through the substantial equivalent 510(k) without clinical data.

And so it's still possible for any new product to require clinical data and maybe the FDA could have a low threshold for requiring that in calling something a new question of safety and effectiveness but then still allow the 510(k) pathway so very similar device types aren't held to that same clinical trial requirement

Dr. Dean: Agreed. Agreed, and I believe that that is in the proposed special controls that we have, that certain testing can be required, especially for in the new materials or new manufacturing processes, we want to understand the effect of those changes.

Dr. Harris: Any other comments or questions? Dr. Li?

Dr. Li: I just want to make sure I'm not confusing myself. So if someone introduces a process product that's in addition to promoting the wound healing you're suggesting but perhaps also claims it's an anti inflammatory or speeds healing, that would not be included in this guideline?

Dr. Dean: That would not be included. So even promoting of wound healing, remember intended use here is to cover the wound, provide a moist environment to allow the natural healing process.

Dr. Li: If it makes any other claim, they would not fall under this guideline.

Dr. Dean: Agreed.

Dr. Li: Okay. Thank you.

Dr. Harris: Any other comments? Dr. DeLong.

Dr. DeLong: Sorry, I'm talking a lot. But just related to the conversation we had earlier about tissue expanders, if all of these were upregulation to Class III, then every manufacturer would have to go out and generate clinical data and it could lead to a dearth of some of these products, particularly in other spaces, I think the vaginal mesh space when they upregulated basically all the manufacturers said it's not financially worth it for us and removed from the market and didn't go through clinical testing for those products, and so you might end up in a position where right now, there's a plethora of products and we don't have great data on all of them but you may end up in a position where you have a very small number of products remaining because all the manufacturers said this isn't worth going through a robust clinical trial to put a fish skin device on the market, or whatever they're using. So –

Dr. Harris: Just to flush out the discussion, if you only had one product on the market and you knew it worked, why do you need two? Why do you need three? Having five products that I don't know work, to me is not a benefit over having one or two that I do know work, in terms of their claims.

Dr. DeLong: That's a very valid point. I am just saying with any up-classification comes access issues. It may end up perfectly, and we have one terrific product and that's the best thing for patients, but it is a consideration.

Dr. Harris: Sure. Dr. Bowman?

Dr. Bowman: Just a quick response to why more than one. Economics, right? If there's a marketplace that has many products, it's going to contain the price, right?

Dr. Harris: We really haven't seen that in wound care.

Dr. Bowman: That might be, but that would be one argument. I know that, you know, in other disease areas, we like more than one treatment option just to give patients the option.

Dr. Harris: Sure. Any other comments? So it sounds as though the committee is in favor of or at least agrees with the special controls as outlined. We've obviously had a discussion around the potential addition of clinical testing, but that I don't know, that's certainly not a majority opinion.

Dr. Dean: Could you clarify your advice on the special controls? So we are, you know, proposing in here that there is testing that will demonstrate substantial equivalence to those that are on the market. There are, as our subject matter expert mentioned, there are tests that are included in this that we tend to look at to ensure that these devices are doing what they say they do. Is there anything else that you would like to see in special controls?

Dr. Harris: Are you speaking to me personally or the panel in general?

Dr. Dean: The panel in general.

Dr. Harris: Anyone? My comment would be that, I actually think that there is tremendous hidden harm in treating patients with products with questionable value. And clinicians have no opportunity to compare one dressing to the other, other than how well it's marketed, perhaps how easily they have access to that product. And delaying treatment in chronic wound care because perhaps it doesn’t trap moisture as well as you would like or

perhaps it does have a low level of immunogenicity I think is harmful and is not – and is impairing the state of health of that patient. So I think these are actually serious products. And what I would personally want to see is a more rigorous demonstration of the product's performance and the ability to compare it's performance to a competitive product so that the decision making that clinicians are making and patients are facing isn't reduced to simply the effectiveness of a company's ability to market a product.

Dr. Dean: Thank you for your input.

Dr. Harris: Okay, so we can move on to our next question if the FDA will read that for the panel.

FDA: Question number three. Please discuss whether you agree with FDA's proposed classification of Class II with special controls for wound dressings with animal derived materials. If you do not agree with FDA's proposed classification, please provide your rationale for recommending a different classification.

Dr. Harris: Any comments? Does anyone feel that the products should not be classified as Class II to special controls? I think you have a unanimous agreement from the panel that the Class II classification seems appropriate.

Dr. Dean: Thank you. Thank you for your input.

Dr. Harris: Thank you. Okay. So we'll move forward and perhaps we can get through our next discussion and take a small break if we're still going. I'd like to now invite the FDA to start the next presentation. And, again, I'll remind the public observers at this meeting that while it is open for public observation, public attendees may not participate except at the specific request of the panel chair. FDA, you may now begin your presentation.

Dr. Zhang: Good afternoon. My name is Min Zhang and I'm a Lead Reviewer in the Division of Infection Control and Plastic Surgery Devices within the Office Surgical Infection Control Devices in CDRH Office of Product Evaluation and Quality.

Today, I will be presenting information regarding our effort to classify absorbable synthetic wound dressing currently product code FRO. This is the outline for my presentation. These are items we will be discussing today. Absorbable synthetic wound dressing is a device intended to cover wound absorb exudate and to maintain appropriate moisture balance within the wound. This type of dressing is composed of absorbable material such as lactide caprolactone polymer, Polydioxanone, or biodegradable polyurethane.

Dressings may contain any animal derived materials, antimicrobial, drugs or biologics. They are often presented in sheet form and are meant to cover wound and reduce the need for frequent dressing changes or to provide a temporary scaffold for cell infiltration. This dressing completely or partially degrade a wound. They are sterile and may be used alone or in conjunction with a secondary non-resolvable wound dressing for securement.

Importantly, they're not intended as a long term skin substitute, a temporary synthetic skin or to accelerate wound healing process. Absorbable synthetic wound dressings have been cleared for prescription use for the following indications for use.

For temporary coverage of non-infected wounds, to maintain a moist wound environment and to be used on several wound types such as partial and full thickness wounds, stage I to IV pressure ulcers, venous ulcers, caused by a mixture of vascular etiologies, venous stasis ulcers, chronic vascular ulcers, diabetic ulcers wounds. [indiscernible]. Partial thickness burns and trauma wounds, cuts, [indiscernible] wounds, surgical wounds, superficial wounds, and

[indiscernible] wounds.

Absorbable wound dressings are preamendment unclassified device type, currently these devices are regulated through 510(k) pathway and cleared for marketing if they're intended use and technology characteristics are substantially equivalent to a legally marketed device. They're a subset of devices currently cleared under product code FRO. As these devices are unclassified, there's no regulation associated with the product code.

To date, FDA has cleared 11 absorbable synthetic wound dressing under product code FRO.

Some clinical background information about wound and wound care. A variety of acute and chronic wounds. Acute wounds can affect anyone and is usually suddenly and heal at a predictable rate. Acute wounds include cuts, post surgical wounds, burns and traumatic wounds. Acute wounds can sometime develop into chronic wounds. Chronic wounds develop over time and do not heal at an rate. Most common chronic wounds are veinous ulcers, diabetic ulcers and pressure ulcers. The pathophysiology of the wound is varied and depend on manufacturers including blood supply, blood pressure, infection and other comorbidities such as diabetes. Patient history, physical examination, and studies including blood work, cultures radiology imaging can be used to [indiscernible] the wound diagnosis. Depending on wound type, the patient may be asking about pain, functional status and quality of life.

Wound treatment is typically managed by applying dressing to cover and protect the wound and maintain a moist wound environment. There's a range of standard of care methods depending on wound types and wound healing progression. There are also a variety of wound care modalities available including compressive dressings, bioengineered dressings, grafts,

negative pressure wound therapy, hyperbaric oxygen and topical drugs.

Various organizations have published guidelines for providing wound care recommendation generally, debridement, [indiscernible] and providing a moist wound environment recommended as part of wound care. Recommendation for dressing selection based on patient specific wound care needs such as the need of [indiscernible] management of prevention fluid loss. Most guidelines don't specify the use of a particular type of wound dressing, and many guidelines conclude that there is little difference in factoring in terms of healing outcomes between dressing types.

A systematic literature review was conducted in an effort to gather any published information regarding the safety and effectiveness of absorbable synthetic wound dressings. The searches were conducted to identify relevant articles published between April 1, 2012 and July 18, 2020. The searches were limited to related to full text publications in English and human studies with a patient member less than 75 excluded. The Systemic literature searches yielded a total of 5,018 initially references. For absorbable synthetic wound dressings together with other wound dressings being presented as classification panel, Including wound dressings with animal derived materials and hemostatic wound dressings with [indiscernible].

However, no articles from systemic searches will determine to be relevant to the safety or effectiveness of the absorbable synthetic wound dressings, therefore, a supplemental search was conducted with more patient member limitation, and seven relevant articles were identified.

Of the seven selected studies, four studies assess the safety of absorbable synthetic wound dressings, one study found no significant difference in complications of infection [indiscernible] under hematoma or seroma between standard of care group which is collogen

wound dressing and absorbable synthetic wound dressing.

One started assessing the use of absorbable glass wound dressing in the diabetic wound care reported less incidence of adverse events and infection of [indiscernible] ulcer standard of care group which was collagen alginate wound dressing. The other two studies reported that no allergic reaction or infections was identified from use of absorbable synthetic wound dressings compared with the standard of care group which was a polyurethane membrane on a split thickness skin graft.

All seven articles reported on device effectiveness for uses in a staged reconstruction of complex wounds as a temporary covering, and a scaffold for Diabetic foot ulcer care., second degree burns, and skin graft donor size, deep partial thickness thermal wounds and [indiscernible] of split thickness skin grafts.

Here is summary of device effectiveness assessment in literature review. In the two studies of fourth stage reconstruction or complex wounds one study reported a significantly lower rate of skin graft failure than the standard of care group, which was collagen.

Another study reported a high integration rate of absorbable synthetic wound dressing [indiscernible] wounds. In the study, for the diabetic food ulcer care, percentage wound error reduction at 12 weeks of the absorbable wound dressing is much higher than the standard of care group, which was collagen [indiscernible] dressing, and it's neuropathic score at 12 weeks is higher in the standard of care group as well.

In the two studies, for 7th degree burns and skin graft donor sites similar healing time and reabsorption was observed for the absorbable synthetic wound dressing and standard of care group, which were hydrophilic polyurethane membrane and a paraffin [indiscernible].

In the study for deep partial thickness thermal wounds, similar scar formation and scar quality were observed for absorbable synthetic dressing and standard of care group which was split thickness skin graft.

In the study for donor sites of split thickness skin grafts similar [indiscernible] and less pain and bleeding were observed for absorbable synthetic wound dressing then standard of care group which was polyurethane foam coated with silicon elastomer. .

Overall, the selected studies from published literature didn't report additional risk of adverse events as compared with the standard of care groups. The absorbable synthetic wound dressing had a similar complication rates, healing time, and [indiscernible] in treatment of different wound types when compared to standard of care groups. The limitation of the literature search include linked publications for the absorbable synthetic wound dressings linked to patient member in the selective studies. And most study when to randomize controlled studies.

The necessary slides background information for medical device reports or MDRs.

For the of time, I won't go through this information in detail since it was summarized previously in the presentation of wound dressing with animal derived materials and product code KGN.

This is a continuation of MDR background and reminder of how MDR can be used. This is a continuation of the MDR background reminder of the limitations. To further contribute to benefit risk assessment of absorbable synthetic wound dressings the agency reviewed individual MDRs for absorbable synthetic wound dressings. Using the FDA's manufacturer and use of facility device experience [indiscernible] database the search identified ten relevant MDRs. Of the ten reports, eight reports were for serious injury and two reports of death. The tables show the

adverse events reported in those identified MDRs. Note that the number of events in the table, you see it's the number of MDRs because multiple adverse events are often reported in each MDR. Note that the individual MDR chooses a category for the event type, which may be serious injury, malfunction, or another category.

This slide provide background information for recourse and medical device recorded base forsake of time, I won't go through this information detail in since it was summarized previously in the presentation for wound dressing with animal derived materials and product code KGN.

The medical device recall database were reviewed for product code FRO as of August 18, 2022.A single report was found for absorbable synthetic wound dressing, the recall was due to misprinting of the expiration date on the packaging. Thus this recall was due to a manufacturing error and doesn't suggest additional risk associated with absorbable synthetic wound dressing as a product class.

To determine the appropriate classification for absorbable synthetic wound dressing we identified risks to health associated with these devices and possible mitigations for these risks. We will be asking the panel for input on the list of risks and mitigations in evaluating the risks to health associated with the use of absorbable synthetic wound dressings.

We consider information from adverse events reported in FDA's MAUDE database the published scientific literature device recall history and FDA's experience in reviewing these devices. FDA has identified the following five risks to health associated with absorbable synthetic wound dressing.

The first risk is toxicity. This can result from device material or degradants of the absorbable material which can be toxic.

The second risk is adverse tissue reaction. This can result from use of device materials including any associated impurities, residues and degradants which are not biocompatible.

The third risk is infection, this can result from inadequate device sterilization or inadequate packaging integrity.

The fourth risk is delay in wound healing. This can result from device materials or degradants of the absorbable materials which may interfere with the wound healing process. This can also result from incomplete biosorption of the dressing into the wound.

The fifth risk is a failure of device integration. This can occur when the dressing, which is intended to provide a temporary scaffold for cellular infiltration does not effectively degrade into the wound and thus resulting in dressing retention in the wound and interference with the wound healing process.

In the right column, we have proposed mitigation measures. We will be addressing through special controls. We believe general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness and sufficient information exists to establish special controls to adequately mitigate risks to health and provide reasonable insurance of device safety and effectiveness for this device type.

To mitigate the risk of toxicity, we recommend biocompatibility evaluation, performance testing, and labeling. To mitigate risk of adverse tissue reaction, we recommend biocompatibility evaluation, performance testing and descriptive information, pyrogenicity testing and labelling. To mitigate risk of infection, we recommend sterilization testing and validation information. Shelf life validation and labeling. To mitigate risk of delay in wound healing, we recommend biocompatibility evaluation, animal performance testing, performance testing and descriptive

information and labeling. To mitigate risk of failure of device integration, we recommend animal performance testing, and labeling.

Here is our proposed classification regulation for absorbable synthetic wound dressing. Part A our regulation defines the device as follows. An absorbable synthetic wound dressing is a device intended to cover a wound to absorb exudate and to maintain appropriate moisture balance within the wound. These devices may additionally be intended as a scaffold for cellular infiltration. It is composed of absorbable synthetic materials such as biodegradable polymers.

Absorbable synthetic wound dressings may be used alone or in conjunction with a secondary non resorbable wound dressing for securement. An absorbable synthetic wound dressing is not intended as a long term skin substitute a temporary synthetic skin or to accelerate the wound healing process. An absorbable synthetic wound dressing does not contain animal derived materials, antimicrobial or drugs or biologics.

Furthermore, we are proposing this device be classified a Class II device with special controls. Based on identified risk and recommended mitigation measures, FDA believes that the following special controls on the next two slides, will provide reasonable assurance of safety and effectiveness for absorbable synthetic wound dressings.

First, performance testing and descriptive information must demonstrate the functionality of the device to achieve the specified use, including establishing the physical and chemical characteristics of a device, the following must be provided. Identity, quantification, and purpose of each component in the finished product. Specification and characterization of each component in the finished product and final release specifications for the finished product.

Second, performance data must demonstrate the sterility of the device.

Third, the device including any degradants must be demonstrated to be biocompatible, nonpyrogenic, and contain endotoxin level within acceptable limits.

Fourth, performance data must support the shelf life of device by demonstrating, continued sterility package integrity and device functionality over the intended shelf life.

Fifth, animal performance testing must demonstrate that the device materials and degradants don't delay the wound healing process and can be appropriately integrated into the surrounding tissue.

Six, performance data must demonstrate that the device performs as intended under anticipated conditions of use including complete degradation of any absorbable materials in the wound and evaluation of expected worst case conditions. The labelling must include the following. A description of the intended user population. Specific instructions regarding the proper placement, sizing, duration of use, frequency of dressing change, maximum use life per application of the dressing, maximum total use life of the dressing and removal of the dressing if applicable.

A list of each ingredient or component within the finished device including the functional role of that ingredient or component within the device. If the device has non resorbable components, a warning statement for the potential retention of those components in the wound or the surrounding area. A contraindication for any known sensitivity to components within the device. A contraindication if there are incompatibilities with other therapies, a shelf life, a statement regarding when to discontinue the use of the device after multiple reapplication based on biocompatibility and performance testing, if applicable.

Any statements in the labelling must be clear such that they may be understood by the

end user supported by appropriate evidence, and consistent with the intended use of covering a wound, absorbing exudate, and maintaining appropriate moisture balance within the wound. Disposal instruction.

This concludes our presentation. Thank you for your time, attention.

Dr. Harris: Thank you. Before we field any clarifying questions from the panel, I'd like to hand the floor to Dr. Dean who has some comments for us.

Dr. Dean: Hi, I just wanted to clarify my earlier comment on special controls and your recommendations for special controls. Please keep in mind that special controls are intended to mitigate the identified risks. So while clinical data can be recommended as a special control, we would like to ask you to tie it back to one of the identified risks that we talked about first before we go into the special controls.

And I also wanted to make the point that because these are pre amendments devices, they were generally considered to be safe and effective prior to 1976, and so our debate should be less about the effectiveness of the devices and more about the risks, mitigations and the risk classification.

Dr. Harris: I just have one comment. I mean, I'm under the impression that part of the reason why FDA is convening this panel is that things have changed since 1976. And that the panel probably wasn't considering fish skin as part of a wound dressing and the like.

And so, it seems like we're at least I'm interpreting this as a bit of, I don't know, that there is on the one hand a desire to update or revisit this classification question, but at the same time, not wanting to revisit too aggressively.

Dr. Dean: I would not put it that way. We certainly we welcome all your comments on these devices. But I just wanted to keep us to the goal of this, which is to classify. And that has to do with the risks, the identified risks, and whether or not those risks can be mitigated through special controls or general controls.

Dr. Harris: Any questions, classifying questions regarding the presentation? Ms. Agazie.

Ms. Agazie: So I have two questions, just an elaboration, the proposed special control mentioned in the presentation, just two I need a little bit more clarification on. Was the performance testing and description information, is that describing the functionality of the product? That's one question. And then another one was the animal testing. So can you elaborate more between the two?

Dr. Dean: For that, I believe I need to ask for Dr. Krause, or one of our subject matter experts.

Dr. Zhang: Yeah, I'm here. So thanks for the question. So yeah, like the – so yeah. The descriptive, like the general information may be like yeah, you know, in addition to like the general [indiscernible] and protection and also like provide the moist environment to for the absorbable synthetic wound dressing and also have some kind of specific claim like to reduce the changing frequency of dressing change frequency, and also sometime have the scaffold claim. So, yeah, we do need like we usually request the company like provide, performance testing to demonstrate like the cell infiltration [indiscernible]. So I'm not sure I answered your question.

Dr. Harris: I think there was a second part to that question.

Ms. Agazie: The second part was the difference between the performance testing and

description and the animal performance testing.

Dr. Zhang: Okay. So the general performance testing. General performance testing we can do like [indiscernible] like material. So to address [indiscernible] especially for absorbable dressing we don't have [indiscernible] we do have some issue. Some degradants cause some toxicity, [indiscernible] a mutagen so we request in vitro bench testing to analyze [indiscernible]degradants and the degradation profile.

For the animal testing, we also like testing degradation to see like impact to wound healing and also, like, support some additional claims like scaffold[Indiscernible] to support specific claims intended use that okay?

Ms. Agazie: Thank you.

Dr. Harris: Dr. Diegelmann.

Dr. Diegelmann: Bob Diegelmann. The number one adverse reaction was pyrogenicity, what kind of testing should be done to test for that?

Dr. Zhang: Okay. Thank you. So yeah, so for the – adverse tissue reaction usually we have like for all the wound dressing, we have like FDA actually have biocompatibility guidance for the different like device types have different biocompatibility test requirements for the tissue reaction. Adverse tissue reactions we can address that through either implantation study or animal study can address the local tissue [indiscernible] such as inflammation, yeah, this kind of stuff.

For pyrogenicity [indiscernible] and also it’s evaluated, it’s going to cause some [Indiscernible]febrile reaction. The pyrogenicity came from two aspects, one is

[indiscernible]material-associated like chemical residue, like the device itself. [indiscernible] Another is bacterial endotoxins. We usually do some [indiscernible] rabbit testing to see use of the device. Cause some like temperature rise [indiscernible]. Did I answer your question?

Dr. Harris: Any other clarifying questions regarding the presentation? So if not, we can move on to the questions.

If FDA is prepared to read the first question, just want to remind the panel if you're having you should have copies of the questions in your packet and continue to remember to identify yourself and unmute your microphone when speaking.

So FDA will read. h, I see a comment. Dr. Galandiuk.

Dr. Galandiuk: I was just going to say when they were mentioning pyrogenicity or things like that, one of the things they could do on animal models would be to measure cytokine release or TMF release. I don't know if they were doing things like that.

Dr. Harris: We can .

Dr. Dean: We are here to elicit your advice. So when we go through the risks, please advise us on any mitigations that we don't have in our proposed special controls.

Dr. Harris: Dr. Li?

Dr. Li: Yes. Steve Li. I'm not sure this is the right time to ask this question, but because we're talking about biodegradable or absorbable polymers, there's a wide range of the rate of degradation or absorbability of these different polymers. So depending on I can imagine that not all wounds heal at the same rate.

So how would you match the degradation rate or the absorption rate with the type of

wound that would be evaluated in your system?

Dr. Harris: Go ahead.

Dr. Zhang: Yeah, that's a good question. For [indiscernible]absorbable wound dressing [indiscernible] degradation profile. It's very different from like three weeks [indiscernible] to more than 1 year. The company may design them to control like how the design material to control theirdegradation rate to like match their intended use. Sometime like the dressing may be acting as a scaffold. So if they want to yeah how. They need to figure out like [indiscernible] match the degradation profile, like duration. Yeah. Sometime [indiscernible] the duration maybe like for several weeks it’s okay. So yeah. Definitely I understand that they are [indiscernible] material biodegradable We only clear a limited number of devices and number of materials. But we are seeing, like, [indiscernible]more biodegradable material [indiscernible]dressings come in. Did I answer your question?

Dr. Li: Pretty much. Just to clarify, so does that mean if I have a product with a certain absorption rate, that I would have a certain intended use or type of wound that I would be using it on? Would that be covered by intended use? How would I match the degradation rate with the kind of wound I'm treating?

Dr. Zhang: Yeah. So now, like, I think like for a wound dressing like actual, [indiscernible] dressings like for absorption rate is very different for the cleared devices, we have the some like specifically for some [indiscernible]to match wound healing process just like intended as like [indiscernible]scaffold or to reduce [indiscernible]change you can leave the dressing [indiscernible]on wound bed. So yeah, Not specified.

Dr. Harris: Okay. So if there are no additional clarifying questions, can we move on to

the panel questions if the FDA will read the first question?

Dr. Zhang: We have the following question for the panel. We are looking for your thoughts and recommendations on the appropriate regulatory classification for the devices. The first question to panel.

FDA has identified in the following table risks to health for absorbable synthetic wound dressing. This identified risks are toxicity, adverse tissue reaction, infection, delay in wound healing, and failure of device integration. Please comment on whether you agree with inclusion of all the risks in the overall risk assessment of absorbable synthetic wound dressings. In addition, please comment on whether you believe that any additional risks should be included in the overall risk assessment of these absorbable synthetic wound dressings.

Dr. Harris: So, comments from the panel regarding the current listing of risk for these absorbable synthetic dressings. Dr. Hunt?

Dr. Hunt: Yes, hi, Kelly Hunt. I was just concerned about the top one just saying toxicity. It just seems too vague. And I think it needs to be specified more in terms of individual toxicities. Thank you.

Dr. Harris: Thank you. Any other comments? Are there any toxicities listed on the proposed listing of toxicities that you think shouldn't be there? Other than perhaps more precision around toxicity. Any new or additional risk? Dr. Bryant.

Dr. Bryant: Nothing new. But it's a recurring theme, with the procedure with wounds infections can happen. So, again, just teasing things out that typically happen versus what can be contributed to the product. Again I just want to make sure I go on record with that again. Thank you.

Dr. Harris: Thank you. Hearing no comments, I will assume that the panel is comfortable with the list of risks that have been identified by FDA and were in the previous table with the one comment perhaps a little bit who are granularity around the risk of quote unquote toxicity. Is that adequate, Dr. Dean?

Dr. Dean: Yes. Thank you for your comments.

Dr. Harris: Great. So now we'll move on to the next question, if FDA will read question number two.

Dr. Zhang: The second question to panel. Section 513 of the Food, Drug, and Cosmetic act states a device should be Class III if insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of its safety and effectiveness and the device is purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury.

A device should be Class II if general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness and there is sufficient information to establish special controls provide such assurance.

A device should be Class I if general controls are sufficient to provide reasonable assurance of the safety and effectiveness or insufficient information exists to determine that general control are sufficient to provide reasonable assurance of the safety and effectiveness or establish special controls provide such assurance but is not purported or represented to be for a use in supporting or sustaining human life or for use which is of substantial importance in preventing impairment of human health and does not present a potential unreasonable risk of

illness or injury.

FDA believes general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness and sufficient information exists to establish special controls to adequately mitigate the risks to health and provide reasonable assurance of device safety and effectiveness for this device type. As such, FDA believes that class II is the appropriate classification for absorbable synthetic wound dressings.

Here is risk mitigation table which outlines identified risk to health for this device type, and recommended controls to mitigate identified risk. Please discuss whether identified special control for absorbable synthetic wound dressings appropriately mitigate the identified risks to health and whether additional or different special controls are recommended.

The proposed special controls will be restated on the next few slides. The first five proposed special control related to performance testing. Number one. Performance testing and descriptive information must demonstrate that the functionality of the device to achieve the specified use including establishing the physical and chemical characteristics of the device. The following must be provided: Identity, quantification, purpose of each component in the finished product. Specification and characterization of each component in the finished product. And final release specifications for the finished product.

Number two, Performance data must demonstrate the sterility of the device.

Number three, the device including any degradants must be demonstrated to be biocompatible, nonpyrogenic, and contain endotoxin level within acceptable limits.

Number four, performance data must support the shelf life of the device by demonstrating continued sterility, package integrity, and device functionality over the identified shelf life.

Number five. Animal performance testing must demonstrate that the device materials and degradants don't delay the wound healing process and can be appropriately integrated into the surrounding tissue.

The sixth proposed special control relates to performance data. Performance data must demonstrate that the device performs as intended under anticipated conditions of use, including complete degradation of any absorbable materials in the wound and evaluation of expected worst case conditions.

The seventh proposed special control relates to labeling. The labeling must include the following. A description of the intended user population. Specific instructions regarding the proper placement, sizing, duration of use, frequency of dressing change, maximum use life per application of the dressing, maximum total use life of the dressing, and removal of the dressing, if applicable. A list of each ingredient or component within the finished device including the functional roles of that ingredient or component within the device. If the device has non resorbable components, a warning statement for the potential retention of these components in the wound or the surrounding area. A contraindication for any known sensitivity to components within the device.

Labeling special control continued: and here we continue with the proposed special control for device labelling. The labelling must include a contraindication if they're incompability with other therapies, a shelf life, a statement regarding when to discontinue the use of the device after multiple application based on biocompatibility and performance testing, if applicable.

Any statements in labelling must be clear such that they may be understood by end user,

supported by appropriate evidence and consistent with intended use of covering a wound, absorbing exudate, and maintaining appropriate moisture balance within the wound. And finally, labelling must include disposal instructions.

Dr. Harris: Thank you. So any comments regarding this question? Dr. Hunt?

Dr. Hunt: Yes, hi. I just had a comment about the degradation of the materials or the absorption. Because there's quite a bit of variability I think in material absorption by patient and also by the type of wound. I think with many absorbable sutures, the surgeons would probably agree that it's highly variable when the patient actually absorbs all the material. And some patients will have material that comes out through the wound that you would have expected to be absorbed quite a long time ago. So there's no real timeline associated with that. So I wondered if there was more detail on that. And then also I have just a similar comment about the previous listing of toxicity, because it's such a broad category. Thank you.

Dr. Harris: Thank you. Dr. Li, do you have any comments about that? It seems like that harkens to an earlier point you were making, Dr. Li.

Dr. Li: Yes. Steve Li. Yeah, I completely agree. There's variation amongst the polymers, just like in the laboratory sense. And then the variation gets even larger when you introduce it into a biological environment. We don't always know what the connection is. So I'm in complete agreement with Dr. Hunt. I'm not exactly sure how you guarantee the match between optimizing the rate of degradation and the rate of healing. I'm not exactly sure how you do that. And, again, I guess just to comment on Dr. Dean's earlier comment that these products have been around for a long time, I'm actually not worried about those. I'm worried about I’m worried about people like me that keep trying to think of something new that you haven't seen before that doesn’t may not

fit into the classification to behave like the classic materials. So I'm really trying to actually reinvestigate the existing ones. I'm trying to protect you from me.

Dr. Dean: I appreciate that. And I will remind you that for new device they would have to go through the 510(k) process and be demonstrated to be substantially equivalent. So we would have some questions if there were differences.

Dr. Harris: Ms. Block?

Ms. Block: I have a question. Because the special class if I indications is asking for animal performance testing. Can the panel request for human performance testing or is that not possible or does that go to clinical trials? Can you explain the difference?

Dr. Dean: You can certainly recommend a special control that involves clinical testing. Again, though, I would tie it back to one of the identified risks and demonstrate how this would mitigate that identified risk to human health.

Ms. Block: So the identified risk would then be the problem or the concern of the degradation between different types of wounds or patient populations, if you will, age. So is that something the FDA would consider since that is our concern?

Dr. Dean: We're here to ask for your advice on any of these risks and the potential mitigation. So if you feel as if the potential mitigations, the special controls that we've set forward are not sufficient, this is the time to identify any additional ones.

Dr. Harris: I'm wondering either Dr. Dean or the content expert, Dr. Zhang, could comment on this issue of the dressing serving as a scaffold for cellular infiltration. That strikes me as having more of a direct interaction between a dressing and the patient that I thought

usually fell within the definition of a device.

Dr. Dean: For that, I would ask Dr. Zhang to respond.

Dr. Zhang: Okay. Yeah. Sorry. Yeah, that's a good question actually. Yeah, we do have lots of internal discussion about for the claim cell infiltration, but finally we think it's [Indiscernible]

Dr. Harris: I'm sorry. I can't. hear your response, can you –

Dr. Zhang: Okay. How about now? Okay. Now. Okay, thank you. Thank you, yeah. So yeah, we have lots comments from the team we do have lots of discussion about this and that's because like we, when we think the cell infiltration and the tissue ingrowth, it's a physical interaction, the infiltration into tissue and ensure it's not like a chemical interaction. So that's why we allow for the synthetic dressing now, because the scaffold claim if you provide animal study to show like the integration of the scaffold the matrix can integrate it into the surrounding tissue. Yeah.

Dr. Harris: So I'll just comment to FDA that my interpretation of that sort of claim will be translated in the clinical setting into this wound this dressing helps wounds heal. And we just went through a discussion about how these dressings don't have that sort of claim, and therefore do not naturally require clinical testing. But when you talk to clinicians about a dressing that's going to have cellular infiltration, it's hard for me not to see that connection being promoted both in the marketing of the product and in people's perception of its use.

Dr. Zhang: Okay. Yeah, that's good question. So actually so for the dressing, if they have a scaffold for the claim, usually, they are used, in the [indiscernible] 2-stage wound construction for the complex wound. So usually like the absorbable synthetic dressing used the

first stage to get the wound bed prepared for the [indiscernible] next step for the skin graft.

Dr. Harris: No, I understand that. And I understand FDA uses wound bed preparation as a defined end point for wound care products. But not for wound dressings. But I thought maybe I don't understand that correctly. But I'm just making that comment in observation so that as you all continue your deliberation which you've obviously been doing, you at least hear that perspective.

Dr. Zhang: Yeah. Thank you. So actually, yeah we like to distinguish between the promotion of the wound healing and if it's like a physical – if it's a biological interaction or a physical interaction. We think that the dressing provides some like physical like matrix. Not provide biological function or like a chemical function for that. That's why I think it's still medical devices is not like chemical function. Thank you.

Dr. Harris: And not to beat a dead horse, but if we're then going to say that the manufacturers need to explain the rationale for all the proponents of these dressings, I would assume they could then explain to you how these “inner materials” are promoting cellular infiltration.

Dr. Zhang: No, they don't have usually they don't say – they just say that in their labeling, just say like scaffold [indiscernible] to prepare the wound bed for the next step for the skin graft? The discussion about how sales impact some [Indiscernible],

Dr. Harris: Dr. Soucek.

Dr. Soucek: Can you hear me?

Dr. Harris: Yes.

Dr. Soucek: I just have to say that every time because I've got a dicey situation. At any rate, just the short answer of saying can you match the degradation to a specific wound or a specific time, probably not ever. You can, like, have a reasonably small range if you control all the variables, which is not possible, because you're talking about changing wounds and changing whatever the biological person there with all the different enzymes and different concentrations. So you can probably range it and how close of a range you can get, maybe you can get through. And but the shorter answer is no. But the other thing I'd like to bring up, you know, this granularity of toxicity, is toxicity the only thing we're really worried about and polymers and complex molecules fall apart. Especially when you are using it as cellular scaffolding.

Because part of these polymers are going to be easily absorbable, biological materials that a clever biopolymer chemist put together to make it not only biocompatible but absorbable. And there's going to be other parts of the molecule that aren't naturally in a human being. So at any rate, those are my thoughts.

Dr. Harris: Thank you. Dr. Galandiuk.

Dr. Galandiuk: Yeah. One should be able to in preclinical studies have standardized models where you can show tissue incorporation or do migration assays or things like that that would be able to be standardized across different products.

Dr. Harris: Thank you. Dr. DeLong?

Dr. DeLong: I just wanted to touch on comments that you were making that I totally agree with that in fact, it seems that there's sort of deceitful marketing practices occasionally where a rep will come to you and say this is device for wound care, it accelerates wound healing, it'll heal your wound super fast. It prevents bacterial contamination, it has antimicrobial

properties, and then you can just ask them any question, they'll say yeah, it does that too. Basically no shame, and you look up their 510(k) and it shows no clinical data, never demonstrated any of these capabilities. And typically FDA mitigates these type of risks with labelling. Nobody takes out the labeling, it's that little document that accompanies the product.

And nobody is reading through that. It's the equivalent of the sheets you have to sign online where you scroll to the bottom and accept. It's not required to be put in front of your face.

So I was wondering if the FDA has any capabilities in terms of being more aggressive about the labelling where each individual packet they have to put in red letters to say this is not designed to accelerate wound healing. This does not have antimicrobial properties, or something like that. It would then be impossible for the physicians to use the product without seeing those limitations that are built into the regulatory framework.

Dr. Dean: You can add that to the list of special controls if you tie it back to one of the risks. And I will remind you that the identified risks are toxicity, adverse tissue reaction, infection delays in wound healing and failure of device integration. If you wish to add any risks to that list, please let us know. But remember that the special controls should link back to those.

Dr. Harris: Any other go ahead.

Dr. DeLong: Is just going to say it doesn't necessarily directly fall under any of those risks, although it's more in appropriate marketing practices. And I don't know if there's a way to prevent that. Devices used improperly where physicians are given unrealistic expectations about the device's performance.

Dr. Dean: Absolutely. We can add requirements about what is in the labelling, as you saw some of the recommended controls included information labelling. And we do look at the

post market environment and look at the claims that are being made.

And we welcome feedback from the public on any claims that they see that go beyond what a device has been cleared or approved for.

Dr. Harris: Thank you. Any other comments regarding we're still talking now about the special controls, correct? So if there are no other comments other than what's been made, seeing as those most of these controls are acceptable to the panel, there's been obviously discussion around granularity of toxicity and perhaps ways to standardize the testing for either immunogenicity or pyrogenicity, but there were no specific recommendations in terms of that.

Dr. Dean: Thank you for your input. We appreciate all of your comments and will look at your concerns including those regarding labelling claims.

Dr. Harris: Perfect. So I believe that was our final question. Or was there one more? We have a third question?

Dr. Dean: We do.

Dr. Harris: I'm sorry. So question number three, if FDA will read that.

Dr. Zhang: The third question to the panel. Please discuss whether you agree with FDA's proposed classification of Class II with special controls for absorbable synthetic wound dressings. If you don't agree with FDA's proposed classification, please provide your rationale for recommending a different classification. This is the end of our presentation for the absorbable synthetic wound dressings.

Dr. Harris: So, does anyone disagree with FDA's proposal that these absorbable wound dressings be Class II medical devices with the associated previously discussed special

controls? So it sounds as though you have unanimous agreement on that proposal.

Dr. Dean: Thank you. This is sufficient for our purposes.

Dr. Harris: Great. Before we move to our next and final presentation for the day, we're going to have a break. It is approximately 4:23 p.m. So why don't we can we come back at 4:45? Great. So little 7th inning stretch. We'll see you in a little bit. Thank you.

[Break]

Dr. Harris: Welcome back everyone. I would now like to invite the FDA to start their final presentation for the day. I'd like to also remind the public observers at this meeting that while the meeting is open to the public for observation, public attendees may not participate except at the specific requests of the panel chair. FDA, you may now begin your presentation.

Dr. Arepalli: Good afternoon. My name is Sam Arepalli and I'm a lead reviewer in the Division of Infection Control and Plastic Surgery Devices within the Office of Surgical and Infection Control Devices in CDRH, the Office of Product Evaluation and Quality.

Today I'll be presenting information regarding our efforts to classify topical hemostatic wound dressings that either contain or do not contain grounding.

These devices are currently unclassified and we are looking for your thoughts and recommendations on the appropriate regulatory classification of these devices.

This is the outline for my presentation. These are the items that I will be discussing today. A topical hemostatic wound dressing without thrombin is intended for external use, often as an adjunct to manual compression to control bleeding and absorb old exudate.

These dressings generally help achieve hemostasis through physical means, such as

creating a physical barrier to stop blood flow, leveraging the absorb to properties of the dressing material to support rapid dehydration and to concentrate platelets and clotting factors at the wound site to aid the natural coagulation cascade.

These dressings can be manufactured from a variety of natural materials including animal derived materials such as collagen and chitosan from shell fish as well as calcium alginate from seaweed, cellulose and [indiscernible]. These dressings can also be manufactured from synthetic materials. For example, synthetic polymers. Many of these dressings are formulated into solid pads or sponges or granules. Example, powder, [indiscernible] while some are formulated as gel and other combined structural material, example gauze with a hemostatic component. Example calcium alginate, chitosan kelvin. Exposure to blood or wound exudate solid or granular topical hemostatic wound dressings may transform into an adhesive gel, which expands and adheres to the wound to control bleeding.

These dressings are not intended for use in the organ space next to internal tissues, veins, arteries, or nerves. Topical hemostatic wound dressings thrombin may contain antimicrobials Example: Chlorhexidine silver which serves to either prevent dressing deterioration, example contamination during shelf storage or to protect the dressing from microbial colonization during use.

A topical hemostatic wound dressing with licensed thrombin is intended for external use for temporary control of moderate to severely bleeding wounds and for control of surface bleeding from vascular access sites and percutaneous catheters or tubes. Such dressings contains thrombin which has been approved through a biologic license application. The license thrombin in these dressings facilitates hemostasis by enhancing the surface activated clotting cascade

through enzymatic cleavage and conversion of fibrinogen to fibrin.

When applied directly on the source of bleeding, these dressings also create a physical barrier to blood flow that may be accompanied by the application of a gentle manual compression to control the bleeding.

Some topical hemostatic wound dressings with licensed thrombin may additionally contain antimicrobial, Example: chlorhexidine silver, which serves to either prevent dressing deterioration, Example: contamination, during shelf storage or to protect the dressing from microbial colonization during use. A topical hemostatic wound dressing without thrombin have been cleared as both prescription and over the counter use devices for helping to control minor bleeding, absorbing body fluid in traumatic, superficial lacerations or wounds. Local management of bleeding wounds such as minor cuts, lacerations and abrasions, temporary treatment of severely bleeding wounds such as surgical wounds is intended for external use, for temporary control of moderate to severely bleeding wounds and for the control of surface bleeding from vascular access sites and percutaneous catheters or tubes. Such dressing contain thrombin which had been approved through a biologic license application. The licensed thrombin is these dressings facilitate homeostasis by enhancing the surface cascade through enzymatic cleavage and conversion/activation without thrombin have been cleared for the following indications for use help control minor bleeding, absorb body fluid in traumatic superficial lacerations or wounds, local management of bleeding wounds such as minor cuts, lacerations and abrasions. Temporary treatment of severely bleeding wounds such as surgical wounds, such as postoperative, donor sites, determine toe logical and traumatic injuries. Temporary external use to stop bleeding of superficial wounds, minor cuts and abrasions in an over the count over the

counter setting, and local management of control of bleeding from per cutaneous needle access, vascular access sites, per cutaneous catheters.

Topical hemostatic wound dressings without thrombin have also been cleared for emergency use as an external temporary traumatic wound treatment to achieve hemostasis for moderate to severe bleeding, for rapid control of bleeding in patients following hemodialysis or patients on anticoagulation therapy. To provide a barrier to bacterial penetration. For control of local wound bleeding, to encourage draining by wicking fluids from a body cavity, infected area or access, and to help remove necrotic tissue from ulcers or other infected wounds when used as wet to dry packing or for local management of moderately to heavily exuding wounds.

Lastly, topical hemostatic wound dressings without thrombin have also been cleared for use on partial and full thickness wounds, pressure ulcers, arterial ulcers venous ulcers, diabetic ulcers, donor sites, traumatic wounds, dermal lesions, surgical incisions including dehisced surgical incisions, draining wounds, lacerations, post laser surgery, podiatric, surgical and traumatic wounds, and other bleeding surfaces, abrasions, surgical debridement sites, skin surface puncture sites, vascular procedure sites, and sites involving percutaneous catheters, tubes and pins.

Topical hemostatic wound dressings with licensed thrombin have been cleared for the following indications of use. Local management and control of surface bleeding from vascular access sites and per cutaneous catheters and tubes. Trauma dressing for temporary control of moderate to severely bleeding wounds an adjunct to manual compression. Reducing time to hemostasis in patients undergoing diagnostic endovascular procedures utilizing 4 – 6 French [indiscernible]

Wound dressings including topical hemostatic wound dressings are a preamendment unclassified device type that have been in commercial distribution since prior to May 28, 1976. These devices are not classified but original classification panels. Currently, these devices are being regulated through the 510(k) pathway and are cleared for marketing if their intended use and technological characters are substantially equivalent to legally marketed predicate device. They are a subset of devices clear under product code FRO.

Since these devices are unclassified, there is no regulation associated with that produce code. FDA has cleared over 100 topical hemostatic wound dressings without Thrombin and 18 topical hemostatic wound dressings with licensed thrombi.

Topical hemostatic wound dressings with and without thrombin contribute to wound hemostasis and are especially important adjuncts to compression and in the control of external hemorrhage. These dressings are used for temporary control of bleeding for a range of topical wounds including minor cuts, lacerations, through severe bleeding in traumatic wounds.

They are commonly used in both military and civilian wounds to control bleeding. External bleeding can be mild, moderate to severe. Moderate to severe bleeding can lead to hemodynamic instability and typically lead to American College of Surgeons Class III or IV hemorrhagic shock. Fifty percent of mortality is attributable to uncontrolled hemorrhage. This clinical condition is the second leading cause of civilian trauma and related mortality. A third of such bleeding is compressible and treated with temporary hemostats which are also used as wound dressing. And two thirds of such bleeding are not compressible. Twenty four percent of deaths may be prevented with prompt effective treatment. Uncontrolled bleeding can result in [indiscernible] hypothermia, hydropathy and acidosis.

Prolonged bleeding can result in multi-system organ failure, secondary to hypertension, sepsis, and excessive transfusions. As there is a wide variety of wound types, there is a range of standard care methods depending on the wound type and wound healing progression. Wounds are typically managed by applying a dressing to cover and protect the wound and maintain a moist wound environment.

Many of these wound dressing devices also frequently serve as hemostatic agents. A selection of specific wound product is made by the surgeon based on surgical judgement. [Indiscernible] approach and the severity of bleeding at the target bleeding site.

Conventional methods of hemostasis include compression, suture ligation clipping and use of energy devices to cauterize bleeding sites. When conventional methods of hemostasis fail or are ineffective or impractical for any severity of external bleeding, topical hemostatic dressings may be used as an adjunct to local compression.

We conducted a literature review to identify any published information pertaining to the safety and effectiveness of topical hemostatic wound dressings both with and without Thrombin under product code FRO. Literature searches were performed to identify all relevant articles for topical hemostatic wound dressings between April 1, 2012 to July 18th, 2022.

The literature searches were performed using multiple search items related to wound dressings with hedges for study design and publication years, and the searched were limited to publications in English. The searches yielded 15 articles, that met the inclusion criteria at the title/abstract level and were retained for full text analysis.

A total of four studies were determined to be relevant to the safety and/or effectiveness of topical hemostatic wound dressings without thrombin and none of these studies that met the

inclusion criteria were relevant to topical hemostatic wound dressings with thrombin.

Here is a brief study of those four studies. One study evaluated time to clotting with and without a hemostatic wound dressing and found the hemostatic wound dressing resulted in significantly shorter time to clot. The same study found no serious complications such as anaphylactic shock, bleeding refractory to manual compression, cutaneous allergy or false aneurysm at the puncture site.

Two studies reported mixed results on whether use of topical hemostatic dressings improve chances of survival in combat situations when compared to no hemostatic wound dressing. Overall, the literature review did not indicate any significant difference in safety between topical hemostatic wound dressings without thrombin and controls.

The use of topical hemostatic wound dressings appear to generally improve clotting time compared to the use of non hemostatic wound dressings. However, the impact on survival was inconclusive.

The next three slides provide background information for medical device reports are MDRs. For the sake of time, I will not go through this information in detail since it was summarized previously in the presentation for wound dressings with animal derived materials under product code KGN.

This is a continuation of MDR background and a reminder of how MDRs can be used. This is a continuation of the MDR background and the remainder of the limitations.

To further contribute to the benefit risk assessment of topical hemostatic wound dressing with or without thrombin, the Agency reviewed individual MDRs for topical wound dressings, with and without thrombin using the FDA's manufacturer and user facility device experience or

MAUDE database from January 1, 1986 to April 1, 2022.

The MAUDE database review for topical hemostatic wound dressings without thrombin resulted in 68 MDRs of which 48 were submitted by manufacturers, 13 voluntarily submitted. Seven reported by user facilities.

Of these, there are 50 serious injuries reported and 15 identified as a malfunction. Note that the individual submitting the MDR chooses the category of the even type, be it serious injury, malfunction or another category.

Of the 68 MDRs, the most commonly reported event was unintentional off label use on internal bleeding with multiple patients requiring reoperation or debridement. Associated with these MDRs were complaints that the dressings did not have enough radiopaque material to be definitively identified on x ray.

Multiple patients experienced skin irritation and blistering that resulted in infection, and one patient suffered what appears to be a chemical burn that led to necrosis. MDR analysis of topical hemostatic wound dressing with thrombin resulted in 15 MDRs reported. There, ten were submitted by manufacturers, four were voluntary submissions and one was submitted by user facility.

Thirteen reported a serious injury, and two reported a malfunction. Of these, multiple patients experience allergic reactions that included redness, disseminating rash that resolve after treatment with antihistamine. Multiple patients reacted with severe symptoms like tachycardia, facial edema, airway constriction, and itching that requires steroid and antihistamine treatment.

In one case, the patient had a and required emergency care, although the underlying causes were not made clear. A pediatric patient required a debridement procedure when the

dressing components formed a hard foreign body that interfered with the healing process.

This slide provides background information for recalls and the medical device recall database. For the sake of time, I will not go through this information in detail since it was summarized previously in the presentation for wound dressings with animal derived materials under product code KGN.

The medical device recall database was queried for product code FRO with no time restriction. Eight recalls were reported for topical hemostatic wound dressing without thrombin. The reason for these recalls include package seal integrity, wrong products packaged together, packaging breach, otherwise known as sterility event, inappropriate claims, and shipping of nonsterile products instead of sterile products.

Four recalls were reported for topical hemostatic wound dressing with thrombin and all were recalled due to packaging defects which may compromise sterility. These recalls are all related to manufacturing errors and do not suggest additional risks related to topical hemostatic wound dressings as a product class.

To determine the appropriate classification for topical hemostatic wound dressings, both without thrombin and with licensed thrombin, we have identified the risks to health associated with these devices and possible mitigations for these risks.

We will be asking the panel for input on the list of risks and mitigations in evaluating the risks to health associate these topical hemostatic wound dressing we considered information from the adverse events reported in the FDA's MAUDE database, the published scientific literature, device recall history and FDA's experience reviewing these devices.

First six of the twelve total risk categories we have identified for hemostatic wound

dressings without thrombin and with licensed thrombin. uncontrolled bleeding can occur when the device does not effectively stop bleeding under anticipated conditions of use. This can also result when the device is used incorrectly. Infection can result from inadequate device sterilization, inadequate viral inactivation, or inadequate packaging integrity.

Adverse tissue reactions can result from the use of device materials that are not biocompatible, delays in wound healing can result from the use of device materials which may interfere with the wound healing process. Transmission of pathogens such as bacteria, mycoplasma, fungi, viruses, and other transmissible agents can result from contaminated animal sources, feed inadequate processing, and viral inactivation of the animal-derived materials

An immunological reaction can result from a device derived from a new animal source or protein denaturation/modification due to the manufacturing conditions. Also, this occurs in certain patients who may be allergic to animal derived materials.

Here are the remaining 6 or the 12 total risk categories we have identified for hemostatic wound dressings without thrombin, and with licensed thrombin, microbial growth within the product during use can occur when the antimicrobial in the dressing does not adequately reduce microbial growth during dressing use Contribution to the spread of antimicrobial resistance can occur when the antimicrobial in the dressing contribute to the selection of organisms and/or limit a clinician's therapeutic options to treat infections.

Foreign body reaction due to retained device can occur when nonabsorbable hemostats are not completely removed from the external target bleeding site resulting in sustained inflammatory response. The end result of such a response is pseudo mass formation requiring invasive diagnostic procedures to rule out tumor or abscess. Such an event can also result in

chronic pain, obstructed blood vessels or compress nerves and compromise function of an extremity.

Rebleeding after attaining hemostasis can occur when there is inadequate adhesive capacity of the hemostat. Precise coverage of the target bleeding site, especially in austere environments may be compromised by temperature extremes, poor lighting, and wind.

Arterial or venous embolism or thrombosis can occur if granular powder or reduced dimension hemostat enters a blood vessel. We believe general controls by themselves are insufficient to provide reasonable issuance of the safety and effectiveness and sufficient information exists to establish special controls to adequately mitigate the risks to health and provide reasonable assurance of device safety and effectiveness for this device type.

Here is a table with the first five items of identified risks. Of the risks listed on the previous slides., and proposed mitigation measures which we propose to be addressed through special controls, to mitigate the risk of uncontrolled bleeding, we recommend material characterization including performance testing, shelf life validation, labelling, and BLA approval for thrombin.

To mitigate the risk of infection, we recommend, sterilization shelf-life validation labelling, and risk management assessment for animal derived materials and BLA approval for thrombin.

To mitigate the risk of adverse tissue reaction, we recommend biocompatibility evaluation, labeling and BLA approval for thrombin.

To mitigate the risk of wound healing we recommend performance testing and descriptive information, biocompatibility evaluation and labeling.

To mitigate the risk of transmission of pathogens such as bacteria, mycoplasma, fungi, viruses and TSE agents, we recommend risk management assessment for animal derived materials, performance testing, labelling, and BLA approval for thrombin.

Here is a table with the remaining seven identified risks and the proposed mitigation measures which will be addressed through special controls.

To mitigate the risk of immunological reaction, we recommend risk management assessment for animal derived materials, performance testing and descriptive information BLA approval for thrombin and labelling.

To mitigate the risk of microbial growth within the product during use. We recommend antimicrobial characterization, and performance testing as well as sterilization validation.

To reduce the risk of contribution to the spread of antimicrobial resistance, we recommend antimicrobial characterization and performance testing AMR risk assessment and labeling.

To mitigate the risk of foreign body reaction due to retained device, rebleeding after attaining homeostasis, arterial or venous embolism, and thrombosis, we recommend performance testing and labelling.

Here is our proposed classification regulation for topical hemostatic wound dressing. Part A of the regulation defines the device as follows. A topical hemostatic wound dressing is a device that is placed externally on skin wounds to temporarily stop or control minor or moderate severe bleeding. This device is not to be implanted, in contact with arteries, veins, nerves, or used on any internals organ or tissue. A topical hemostatic wound dressing does not contain drugs.

Subpart 1. Refers to topical hemostatic wound dressing without thrombin, and is defined as follows. Topical hemostatic wound dressing without thrombin is intended for external use to temporarily control bleeding and absorb wound exudate. This device helps achieve hemostasis through only physical, that is not chemical, means such as creating a physical barrier to stop blood flow and absorbing moisture. A topical hemostatic wound dressing without thrombin may contain animal derived materials for structural moisture retention purposes. Additionally, a topical hemostatic wound dressing without thrombin may contain an antimicrobial of low or medium antimicrobial resistance risk such as preserved to protect contamination or activation of the dressing during shelf storage or a protectant, example to protect the dressing from microbial colonization during use. Such dressing does not contain any biologics including thrombin or antimicrobial of high AMR risk.

Subpart two refers to hemostatic wound dressing with licensed thrombin. A topical hemostatic wound dressing with licensed thrombin is intended for internal use to control bleeding. The device creates a physical barrier to blood flow through the application of adjunctive manual compression and the thrombin in the device facilitates hemostasis by enhancing the surface activated clotting cascade through enzymatic cleavage and conversion fibrinogen to fibrin. A topical hemostatic wound dressing with licensed thrombin, may additionally contain an antimicrobial of medium or low AMR risk as a preservative. Example, to prevent contamination or deterioration of the dressing during shelf storage. Or a protectant that is, for example, to protect the dressing from the microbial colonization during use. Such dressing does not contain any biologics other than licensed thrombin or antimicrobials of high AMR risk.

Furthermore, we are proposing these devices be classified as Class II devices with special

controls. Based on the identified risks and recommended mitigation measures

FDA believes that the following special controls on the next eight slides provides reasonable assurance of safety and effectiveness for hemostatic wound dressings without thrombin and with licensed thrombin. Please note that the special controls for the hemostatic wound dressing without thrombin, are the same as those for hemostatic wound dressings utilizing thrombin except for special control number two and for one exception in the labeling which apply only to hemostatic wound dressings utilize thrombin and which I will clearly indicate as I talk through the special controls.

The special controls for this device are. Number one, performance testing and descriptive information must demonstrate the functionality of the device to achieve the specified use, including establishing the physical and chemical characteristics of the device. The following must be provided. Identity, quantification, and purpose of each component in the finished product.

Number two, specification and characterization of each component in the finished product.

And finally, number three, final release specifications for the finished product.

So number two. For the hemostatic wound dressings with licensed thrombin, the licensed thrombin component must be licensed through approved biologics license application and must function in the device consistent with BLA approved indications and usage.

Number three. Performance data must demonstrate the sterility of the device.

Number four, device must be demonstrated to be biocompatible.

Number five, performance data must support the shelf life of the device by demonstrating continued sterility, package integrity, and device functionality over the identified shelf life.

Number six, performance data must demonstrate that the device performs as intended under anticipated conditions of use, including evaluation of expected worst case conditions and must characterize number one, amount of swelling. Change in volume or change in weight of the device.

Number two, in vitro clotting time.

Number three, absorption of the device under physiologically relevant conditions if the device is resorbable.

Number four, in vivo time to hemostasis rate of rebleeding, failed hemostasis, effectiveness hemostasis in the presence of coagulopathy, effectiveness in patients on anticoagulation therapy if indicated uniform definition of hemostasis.

Number five. Amount of device retained in that wound.

Number six. Reliable adhesion to the target bleeding site for different bleeding severities.

And finally, number seven, risk of thrombosis and embolization if the product contains powder or granules.

Number seven, For devices containing animal derives materials, the following information must be provided to support the safety of the non-thrombin animal derived materials.

Number one, documentation of the processing methods including animal husbandry using selection as well as methods for tissue storage, transport, and quarantine that mitigate the risk of parasites and pathogens.

Number two, performance data which demonstrates adequate removal, that is clearance and inactivation of parasites and pathogens including bacteria, mycoplasma, fungi, viruses and other transmissible, spongiform and encephalopathy agents from the final finished device.

Number three, risk management assessment for the inclusion of animal derived materials which considers any probable risk associated with the presence of the animal tissue in the final finished solid wound dressing including pathogen and parasite infection and immunological reaction. The risk management assessment must describe how these risks are controlled and mitigated by A, the methods of animal husbandry, tissue selection, and tissue handling. B, manufacturing and process controls. C, data documenting the ability of the manufacturing and sterilization procedures to ensure adequate removal, that is clearance and inactivation, of parasites and pathogens from the final finished device.

Number eight, for devices containing antimicrobials, antimicrobial characterization and performance data must include the following.

Number one, performance data must demonstrate that each antimicrobial has a purpose and is present in appropriate amount to perform and intended under anticipated conditions of use and storage conditions including evaluation of worst-cast conditions. If the antimicrobial is present as a microbial barrier, microbial barrier testing must be conducted to demonstrate the inhibition of passage of microorganisms through the product.

If antimicrobial is present to inhibit microbial growth within the product during use antimicrobial effectiveness testing must be conducted to demonstrate inhibition of microbial growth within the product during use.

The testing must include, A, establishment of minimum effectiveness concentration or

MEC, of the final product under worst case conditions. B, identification of the period of effectiveness, maximum product use life, based on concentration of antimicrobial, leachability data, and performance under worst case simulated conditions. C, for solid topical hemostatic wounds dressings, Example, pads and gauze containing antimicrobials performance evaluation should be conducted with clinically relevant strains including available strains of challenge organisms containing specific antimicrobial resistance mechanisms as parts worst case scenario performance testing for topical hemostatic wound dressings containing antimicrobial and formulated as gel, cream, ointment, powder or granules, preservative effectiveness testing must be conducted on at least three different manufactured lots of the final finished device that has been real time aged for the stated shelf life.

If the dressing is a multiple use product, the test articles should also be conditioned based on worst case simulated use for maximum use life.

Number two, evaluation and identification of any probable risk of potential contribution to the development and spread of antimicrobial resistance must include identification of each antimicrobial proposed mechanism of action and justification of its status as not medically important.

B, AN AMR risk assessment for each antimicrobial including the following characterization elements ,known resistance mechanisms, transmissibility of resistance, list of resistant microbial species and location of isolation or contribution to medically important antimicrobial resistance.

Number nine. Labelling must bear all information required for the safe and effective use of the device, especially including the following.

Number one, a description of the intended user population.

Number two, specific instructions regarding the proper placement, sizing, duration of use, frequency of dressing change, maximum use life per application of the dressing, maximum total use life of the dressing, and removal of the dressing or approximate absorption rate if applicable.

Number three, instruction to inspect the wound after dressing removal to remove any residual dressing material that may be left in the wound.

Number four, a list of each ingredient or component within the finished device including the functional role of ingredient or component within the dressing.

Number five, if the dressing is non resorbable, the warning statement for the potential retention of material in the wound or the surrounding area.

Number six, the concentration or amount of thrombin present in the product.

Number seven, for hemostatic wound dressings, the presence of thrombin, labeling must include warnings, precautions and contraindication indications associated with thrombin as stated in the approved BLA.

Number eight, Warning severe bleeding or when vasculature is exposed, caution should be taken when using dressings in powder or granular form at the bleeding site as there is a risk of causing embolization.

Number nine, a contraindication for any known sensitivity with components within the dressing.

Number ten, a contraindication if there are incompatabilities with other therapies.

Number eleven, a warning that the device is not intended for control of internal bleeding.

Number twelve, a shelf life.

Number thirteen, storage conditions.

Number fourteen, a statement regarding when to discontinue use of the device after multiple reapplications based on biocompatibility and performance testing if applicable.

Number 15, for devices indicated for over the counter use, the indications must specify conditions, uses, or purposes for which the product may be safely administered by a lay user without the supervision of a licensed practitioner.

Number 16, disposal instructions.

Number ten, for devices containing antimicrobial, labeling must also include one, statement of the role of the antimicrobial in the products. Two, specific instructions regarding how and when to properly dispose of the product. And when not to use the product. Three, a statement of general effectiveness such as antimicrobial and antibacterial or microbial barrier without listing specific test organisms or log reduction values. And number four, a statement explaining the effectiveness of antimicrobial in affecting wound bioburden has not been evaluated or established.

Thank you. This concludes our presentation. Thank you for your time and attention.

Dr. Harris: Thank you. So now we'll take any classifying questions from the panel. Okay. If there are no clarifying questions, we will move on to the panel questions and our deliberations. At this time, I'll want to remind members to identify yourself when you speak, make sure your microphone is unmuted, and you can find a copy of the questions in your packet.

FDA, if you will please read question number one.

FDA QUESTIONS

Dr. Arepalli: We have the following questions for the panel. We are looking for your thoughts and recommendations on the appropriate regulatory classification for these devices.

For question one, we refer you to the risks of the topical hemostatic wound dressings both without thrombin and with the licensed thrombin. Uncontrolled bleeding, infection, adverse tissue reaction, delay in wound healing, transmission of pathogens and parasites, immunological reaction, microbial growth within the product during use, contribution to the spread of antimicrobial resistance, foreign body reaction due to retained device, rebleeding after attaining hemostasis, arterial or venous embolism, and thrombosis.

Please comment on whether you agree with inclusion of all the risks in the overall risk assessment of topical hemostatic wound dressings both without thrombin and with licensed thrombin.

In addition, please comment on whether you believe that any additional risks should be included in the overall risk assessment of these topical hemostatic wound dressings.

Dr. Harris: Okay. We'll open it up for discussion. Does anyone feel that there are additional risks that they can think of that should be added to that list which was just reviewed for us? Or are there any risks on that list that you think should be removed? Dr. McGrath.

Dr. McGrath: Can I just ask one question? With regard to the embolism and thrombosis, is there evidence that it's possible when you are doing – do we know if you use granular or powder thrombotics on top of a blood vessel that you could end up with embolism and DVT?

Dr. Dean: That's an identified risk.

Dr. Harris: I think you're saying have there been reported cases of such?

Dr. McGrath: Yeah.

Dr. Harris: Can we have our content expert or Dr. Dean answer that question?

Dr. Dean: Yes. I'd like to refer to either Dr. Krause or Dr. Arepalli.

Dr. Krause: This is David Krause. There was a report on the CBER website where if the hemostatic agent is applied with pressure that it could cause an embolism. And when I say pressure, the pressure was air pressure. I think Dr. Gibeily if he's on might be able to further elaborate.

Dr. Dean: He may be in the audience and not able to unmute.

Dr. Krause: Let me take a look.

Dr. Bloom: While you're waiting to look, so, we certainly talk about air embolism events when we're dealing with procedures blood vessels and we talk anecdotally about particles being sucked in. I don't know if it's ever been – certainly in my experience, I've never seen it. I can't pull any literature on it, but we talk about it. And I guess anytime you're dealing with an open blood vessel, there's a risk of – because of air pressure, getting sucked in. And if it is a procoagulant like one of these agents, it could lead to an arterial thrombosis, or be a thrombosis for that matter.

Dr. Krause: Right. There were, reports on the CBER website of this actually occurring but it's rare, so I think we put it on there because there are some reports that it has happened, and we thought it would be something we wanted to make sure was addressed.

Dr. Harris: Any other questions or comments? Dr. Diegelmann.

Dr. Diegelmann: Bob Diegelmann here. The Army Institute for Surgical Research did a study where they put WoundStat, which is a granular product of sodium bentonite into a carotid artery and saw one of 12 pigs, I believe, had a piece of the woundStat into the artery. And that may be why they have that risk associated with that granular powder.

Dr. Harris: Thank you. Any other questions or comments about the list of risks identified associated with these topical hemostats with or without thrombosis? So it sounds like the committee is comfortable with the list of risks that have been proposed by FDA for this class of products. Is that sufficient for you, Dr. Dean?

Dr. Dean: Yes, thank you.

Dr. Harris: So, then we will move on to

Dr. Dean: Actually, I apologize. I do have one question. If we could bring George Gibeily into the group so that he can say something.

Dr. Harris: Certainly.

Dr. Bryant: In the interim, Dr. Krause: If with he could confirm specifically [indiscernible] which was articulated earlier, which was the concern around air. And let's make sure we get that clear.

Dr. Harris: As the item is being embolized, is that what you're saying?

Dr. Bryant: Yes.

Dr. Harris: Okay. All right.

Dr. Gibeily: George Gibeily. I'm general surgeon. And an FDA Medical officer for the Plastic and Reconstructive surgery. Yes indeed, there are a number of reports of use of powder on

large surface areas soft tissue bleeding which frequently is low pressure venous, low flow bleeding whereby not only thrombosis but also embolism occurred.

Additionally, one of the indications it's used on catheter sites and venous access sites. catheter sites with 4 – 6 French catheters, and when applied topically, maybe not a big deal, but when applied into the catheter site, these powdered and granular hemostats had a clear potential risk of embolization. So yeah, I think that's that and perhaps junctional bleeding.

Someone mentioned Exstat that time. We have cleared that as a class two device because of military need. It's difficult to get enough patients in a clinical study with junctional bleeding. But this device underwent rigorous animal studies. Models, that modeled junctional bleeding , and those of you that know ex stat, it is a cellulose sponge which expands up to five centimeters with exposure to blood. It is least likely to embolize, but certainly granular hemostats can, it has been described. I just wanted to mention that.

Dr. Harris: Thank you, Dr. Gibeily.

Dr. Gibeily: Thank you

Dr. Harris: So, I don't know if anyone – of our content experts or Dr. Gibeily could address Brian's question regarding risk of potential air embolism associated with the use of these products. Is that the question, Dr. Bryant?

Dr. Bryant: LaMont Bryant. It was to confirm what was posted on the website to make sure the panelists have the facts associated with what was on the FDA website. Specifically around application through – associated with air.

Dr. Gibeily: Thank you for that question, Dr. Bryant in fact, most of these hemostats

are applied without a propulsion agent. That could be CO2 or air. But there are some that have been submitted to FDA that do in fact have a propulsion agent where the gas embolism as well as device embolism becomes a greater risk and certainly something that we need to look at. At least in the preclinical studies. We would assess for that with things like transesophageal ultrasound looking for air entering the right ventricle. Certainly [indiscernible]evidence and histologic evidence of ischemia resulting from air embolism, and all that is written into the animal studies that that we do review. But that's a really important question.

Dr. Bryant: That answers my question, just to make sure it was clear.

Dr. Krause: I just wanted to add that the CBER website does include a limit to how much pressure can be used. I'm thinking it's around eight pounds, but I'm not sure exactly. Need to spend some time, go look on the website. Maybe we can do that and tell you later if we can find it.

Dr. Harris: Thank you, Dr. Krause. So, if there are no other comments regarding risks associated with these devices? Then I believe the panel is comfortable with those listed risks. Is that sufficient for you, Dr. Dean?

Dr. Dean: That is. Thank you for the input on the risks.

Dr. Harris: So, if we could have FDA read question number two.

Dr. Arepalli: Question two. Section 513 of the Food, Drug, and Cosmetic Act states a device should be Class III if insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of safety and effectiveness and if the device is purported or represented to be for use in supporting or sustaining human life, or for a use which is of substantial importance in preventing in impairment of human health, or if the

device presents a potential unreasonable risk of illness or jury.

A device should be Class II if general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness and there is sufficient information to establish special controls to provide such assurance.

A device should be Class I if general controls are sufficient to provide reasonable assurance of the safety and effectiveness or insufficient information exists to determine that general controls are sufficient to provide reasonable assurance of the safety and effectiveness or establish special controls to provide such assurance but is not purported or represented to be used in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health and does not present a potential unreasonable risk of illness or jury.

FDA believes general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness and sufficient information exists to establish special controls to adequately mitigate risks to health and provide reasonable assurance of device safety and effectiveness for this device type. As such, FDA believes that Class II is the appropriate classification for topical hemostatic wound dressings.

The following table outlines the identified risks to health for topical hemostatic dressings devices without thrombosis and recommended controls to mitigate the identified risks. To mitigate the risk of uncontrolled bleeding, we recommend material characterization, including performance testing, shelf life validation and labeling.

To mitigate the risk of infection, we recommend sterilization, shelf life validation, labelling and risk management assessment for animal derived materials.

To mitigate the risk of adverse tissue reaction, we recommend biocompatibility evaluation and labeling.

To mitigate the risks of delays in wound healing, we recommend perform testing and descriptive information, biocompatibility evaluation and labelling.

To mitigate the risk of transmission of pathogens such as bacteria, mycoplasma fungi, viruses, and other transmittable agents we recommend risk management assessment for animal derived materials, performance testing and labelling.

To reduce the risk of immunological reaction, we recommend risk management assessment for animal derived materials, performance testing and descriptive information and labelling.

To mitigate the risk of microbial growth within the product during use, we recommend antimicrobial characterization, performance testing as well as sterilization validation.

To mitigate the risk of contribution to the spread on antimicrobial resistance, AMR, we recommend antimicrobial characterization and performance testing and antimicrobial risk assessment, and labeling.

To mitigate the risk of foreign body reaction due to retained device, rebleeding after attaining hemostasis, arterial or venous embolism and thrombosis, we recommend performance testing and labelling.

Question two A. Please discuss whether the identified special controls for hemostatic wound dressings without thrombin appropriately mitigate the identified risks to health and whether additional or different special controls are recommended.

The special controls for the device are, number one, performance testing and descriptive information must demonstrate the functionality of the device to achieve the specified use, including establishing the physical and chemical characteristics of the device. The following must be provided. Identity, quantification, and purpose of each component in the finished product. Specification and characterization of each component in the finished product. And final release specifications for the finished product.

Number two. Performs data must demonstrate the sterility of the device.

Number three, device must be demonstrated to be biocompatible.

Number four, performance data must support the identified shelf life of the device by demonstrating continued sterility, package integrity and device functionality over the identified life-span.

Number five, performance data must demonstrate that the device performs as intended under anticipated conditions of use, including evaluation of expected worst case conditions and must characterize, number one, amount of swelling, that is change in volume or change in weight of the device. Two, in vitro clotting time. Three, absorption of the device under physiologically relevant conditions if the device is re-absorbable. Four, time to hemostasis, rate of rebleeding, failed hemostasis, effectiveness of hemostasis in presence of hydropathy, effectiveness in patients on anticoagulation therapy if indicated, uniform definition of hemostasis. Five, amount of device retained in the wound. Six, reliable adhesion to the target bleeding site for different bleeding severities. Seven, risk of thrombosis and embolism if the product contains powder or granules.

Number six, for devices containing animal derived materials, the following information

must be provided to support the safety of the non-thrombin animal derived materials.

One, documentation of the processing methods including animal husbandry and tissue selection as well as methods for tissue storage, transport, and quarantine that mitigate the risk of parasite and pathogens.

Two, performance data must demonstrate adequate removal, that is clearance or inactivation of parasites and pathogens including, bacteria, mycoplasma, fungi, viruses and other transmissible spongiform encephalopathy agent from the final finished device.

Three, risk Management assessment for the inclusion of animal-derived materials, which considers any probable risk associated within the presence of the animal tissue in the final finished solid wound dressing including pathogens and parasite infection and immunological reaction.

The risk management assessment must describe how these risks are controlled and mitigated by. A, the methods of animal husbandry, tissue selection, and tissue handling. B, manufacturing and process controls and C, data documenting the ability of the manufacturing and sterilization procedures to ensure adequate removal, that is clearance or inactivation of parasites and pathogens from the final finished device.

Number seven, for devices containing antimicrobials antimicrobial micro characterization, performance data must include the following. One, performance data must demonstrate that each antimicrobial has a purpose and is present in appropriate amounts to perform as intended under anticipated conditions of use and storage conditions including evaluation of worst case conditions. If the antimicrobial is present as a microbial barrier testing, microbial barrier testing must be conducted to demonstrate inhibition of passage of

microorganisms through the product, if the antimicrobial is present to inhibit microbial growth within the product during use, antimicrobial effectiveness testing must be conducted to demonstrate inhibition of microbial growth within the product during use.

This testing must include A, establishment of minimum effectiveness concentration or MEC of the final product under worst case conditions. B, identification of product of the period of effectiveness, that is maximum product use life based on concentration of antimicrobial, leachability data and performance under worse case simulated use conditions. C, for solid topical hemostatic wounds dressings, pads gauze containing antimicrobial, performance evaluation should be conducted with clinically relevant strains, including available strains of challenge organisms containing specific antimicrobial resistance mechanisms as part of worst case scenario performance testing.

For topical hemostatic wound dressings containing antimicrobials and formulated as gels, creams, ointment, powder granules, preservative effectiveness testing must be conducted on at least three different manufactured lots of the final finished device that has been real time age for the stated shelf life. If the dressing is a multi-use product, the test article should also be conditioned based on worst case simulation use for maximum use life.

Two, evaluation and identification of any probable risk for potential contribution to the development and spread of antimicrobial resistance, that is AMR, must include A, identification of each antimicrobial, proposed mechanism of action, and justification of its status as not medically important. B, an AMR risk assessment for each antimicrobial including the following characterization elements known resistance mechanisms, transmissibility of resistance, list of resistant microbial species, and location of isolation or contribution to medically important

antimicrobial resistance.

Number eight, labelling must bear all information required for the safe and effective use of the device, specifically including the following. One, a description of the intended user population. Two, specific instructions regarding the proper placement, sizing, duration of use, frequency of dressing change, maximum use life per application of the dressing, maximum total use life of the dressing, and removal of the dressing if applicable.

Three, instructions to inspect the wound after dressing removal to remove any residual dressing material that may be left in the wound.

Four, a list of each ingredient or component within the finished device including the functional role of that ingredient or component within the device.

Five, if the device is non resorbable, a warning statement for the potential retention of material in the wound or the surrounding area.

Six, a contraindication for any known sensitivity to components within the device.

Seven, a contraindication if there are incompatabilities with other therapies.

Eight, a warning that the device is not intender control of internal bleeding.

Nine, a warning that for severe bleeding, or when vasculature is exposed, caution should be taken when using dressings in powder or granular form at the bleeding site as there is a possibility of causing embolization.

Ten, a shelf life.

Eleven, a statement regarding when to discontinue use of the device after multiple reapplications based on biocompatibility and performance testing, if applicable.

Twelve, for devices indicated for over the counter use, the indications must specify conditions uses or purposes for which the product may be safely administered by a lay user without the supervision of a licensed practitioner.

Thirteen, disposal instructions.

Number nine, for devices containing antimicrobials, the labelling must also include, one, statement of the role of the antimicrobials in the product. Specific instructions regarding how and when to properly dispose of the product. A statement of general effectiveness such as antimicrobial, antibacterial, or microbial barrier without listing specific test organisms or log reduction values. Four, a statement explaining that the effectiveness of the antimicrobial wound bio-burden has not been evaluated or established.

For question 2B, we turn to topical hemostatic wound dressings with licensed thrombin. The FDA has identified the following risks to health and mitigation for topical hemostatic wound dressings devices, with licensed thrombin.

To mitigate the risk of uncontrolled bleeding, we recommend material characterization, including performance testing, shelf-life validation, and labelling, and BLA approval for thrombin

To mitigate the risk of infection, we recommend sterilization, shelf life validation, labeling, and risk management assessment for animal derived materials, and BLA approval for thrombin.

To mitigate the risk of adverse tissue reaction, we recommend biocompatibility evaluation, labeling, and BLA approval for thrombin.

To mitigate the risk of delays in wound healing we recommend performance testing and descriptive information biocompatibilities evaluation and labelling.

To mitigate the risk of transmission of pathogens such as bacteria, mycoplasma, fungi, viruses, and TSE agents, we recommend risk management assessment for animal derived materials, performance testing, labeling and BLA approval for thrombin.

The special controls for this device are. Number one. performance testing and descriptive information must demonstrate the functionality of the device to achieve the specified use, including establishing the physical and chemical characteristics of the device.

The following must be provided. One, identity, quantification, and purpose of each component in the finished product.

Two, specification and characterization of each component in the finished product.

Three, final release specifications for the finished product.

Number two, for hemostatic wound dressings with licensed thrombin, the thrombin component in the device must be licensed through an approved biologics license application or BLA and must function in the device consistent with the BLA-approved indications and usage.

Number three, performance data must demonstrate the sterility of the device.

Number four, device must be demonstrated to be biocompatible.

Number five, performance data must support the shelf life of the device by demonstrating continued sterility, package integrity, and device functionality over the identified shelf life.

Number six, performance data must demonstrate that the device performs as intended under anticipated conditions of use, including evaluation of expected worst-case conditions, and

must characterize one, amount of swelling, that is change in volume or change in weight of the device. Two, in vitro clotting time. Three, absorption of the device under physiologically relevant conditions if the device is resorbable.

Four, in vivo time to hemostasis, rate of rebleeding, failed hemostasis, effectiveness of hemostasis in the presence of coagulopathy. Effectiveness in patients on anticoagulation therapy if indicated, uniform definition of homeostasis.

Five, amount of device retained in the wound.

Six, reliable adhesion to the target bleeding site for different bleeding severities.

Seven, risk of thrombosis and embolization if the product contains powder or granules.

Number seven, for devices containing animal derived materials, the following information must be provided to support the safety of the non-thrombin animal-derived materials.

One, documentation of the processing methods including animal husbandry and tissue selection as well as methods for tissue storage, transport, and quarantine that mitigate the risk of parasite and pathogens.

Two, performance data which demonstrates adequate removal, that is clearance or inactivation of parasites and pathogens, including bacteria, mycoplasma, fungi, viruses, and other transmissible spongiform encephalopathy agents from the final finished device.

Three, risk management assessment for the inclusion of animal-derived materials which considers any probable risk associated with the presence of the animal tissue in the final finished solid wound dressing including pathogens and parasite infection and immunological reaction.

The risk management assessment must describe how these risks are controlled and mitigated. A, the methods of animal husbandry, tissue selection, and tissue handling. B manufacturing and process controls. C, data documenting the ability of the manufacturing and sterilization procedures to ensure adequate removal, that is clearance and inactivation of parasites and pathogens from the final finished device.

Number eight, for the devices containing antimicrobials. Antimicrobial characterization and performance data must include the following.

One, performance data must demonstrate that each antimicrobial has a purpose and is present in appropriate amounts to perform as intended under anticipated conditions of use and storage conditions including evaluation of worst-case conditions. If the antimicrobial is present as a microbial barrier, microbial barrier testing must be conducted to demonstrate inhibition of passage of microorganisms through the product. If the antimicrobial is present to inhibit microbial growth within the product during use, antimicrobial effectiveness testing must be conducted to demonstrate inhibition of microbial growth within the product during use.

The testing must include A, establishment of the minimum effective concentration or MEC of the final product under worst-case conditions. B, identification of a period of effectiveness maximum product use life based on concentration of antimicrobial, leachability data, and performance under worst-case simulated use conditions.

C, for solid topical hemostatic wound dressings, that is pads, gauze, containing antimicrobials, performance evaluation must be conducted with clinically relevant strains including available strains of challenge organisms containing specific antimicrobial resistance mechanisms as part of wort case scenario performance testing.

For topical hemostatic wound dressings containing antimicrobial, and formulated as gel, cream, ointment, powder, or granules, preservative effectiveness testing must be conducted on at least three different manufactured lots of the final finished device that has been real time aged for stated shelf life. If the dressing is a multiple use product, the test articles should also be conditioned based on worst case simulated use for maximum use-life.

Two, evaluation and identification of any probable risk of potential contribution to the development and spread of antimicrobial resistance, that is AMR, must include, A, identification of each antimicrobial, proposed mechanism of action and justification of status as not medically important.

B, an AMR risk assessment for each antimicrobial, including the following characterization elements: known resistance mechanisms, transmissibility of resistance, list of resistant microbial species and location of isolation or contribution to medically important antimicrobial resistance.

Number nine. Labelling must bear all information required for the safe and effectiveness use of the device. Specifically including the following. One, a description of the intended user population.

Two, a statement that the device is intended for topical, temporary, less than 24 hours control of bleeding. Specific instructions regarding the proper placement, sizing, duration of use, frequency of dressing change, maximum use life per application of the dressing, maximum total use life of the dressing, and removal of the dressing or appropriate reabsorption rate if applicable.

Four, instruction to inspect the wound after dressing removal to remove any residual

dressing material that may be left in the wound.

Five, a list of each ingredient or component within the finished device, including the functional role of that ingredient or component within the device.

Six, if the device is non resorbable, a warning statement for the potential retention of material in the wound or the surrounding area.

Seven, the concentration or amount of thrombin present in the product.

Eight, warnings, precautions, and contraindications associate with the thrombin as stated in the approved BLA.

Nine, a warning that for severe bleeding, or when vasculature is exposed, caution should be taken when using dressings in powder or granular form at the bleeding site, as there is a risk of causing embolism.

Ten, a contraindication for any known sensitivity to components within the device. A contraindication if there are incompatabilities with other therapies.

Twelve: a warning that the device is not intended for control of internal bleeding.

Thirteen, a shelf life.

Fourteen:, storage conditions.

Fifteen, a statement regarding when to discontinue use of the device after multiple reapplications based on biocompatibility and performance testing if applicable.

Sixteen, for devices indicated for over the counter use, the indications must specify conditions, uses, or purposes for which the product may be safely administered by a lay user

without the supervision of a licensed practitioner.

Seventeen, disposal instructions.

Number ten. for devices containing antimicrobials, the labelling must include, one, statement of the role of the antimicrobials in the product.

Two, specific instructions regarding how and when to properly dispose of the product.

Three, a statement of general effectiveness such as antimicrobial, antibacterial, or microbial barrier without listing specific test organisms or log reduction values.

Four, a statement explaining that the effectiveness of the antimicrobial in affecting wound bioburden has not been evaluated or established.

Dr. Harris: Thank you. Before we discuss that question, I'd like to give the floor to Dr. Krause who has some follow up regarding the question regarding air embolism.

Dr. Krause. Yeah. Thank you. I just did a little quick research. And it was a report of air or gas embolism occurring immediately or after application of hemostatic drugs or biological products using air or gas pressurized sprayers and the warnings and precautions are listed on products like Evicel, and Arista and there may be others. but those are the ones that were in the warning when it was published in 2010. That was just a follow up. Thanks for letting me provide that.

Dr. Harris: Thank you. So you've had time to digest the question. Does anyone have any comments or questions regarding this special controls as nicely outlined?

If there are no questions, I will assume that the panel is comfortable with the special controls as detailed for these topical hemostats both with and without licensed thrombin. Is that

sufficient, Dr. Dean?

Dr. Dean: Yes, thank you for your input on the special controls.

Dr. Harris: Perfect. Well, we have a final question, which I understand is a little shorter. If FDA will read question number three.

Dr. Arepalli: Please discuss whether you agree with FDA's proposed classification of Class II with the special controls for a topical hemostatic wound dressing without thrombin and a topical hemostatic wound dressing with the licensed thrombin. If you do not agree with FDA's proposed classification, please provide your rationale for recommending a different classification.

Dr. Harris: Thank you. Any comments regarding the proposed classification of these topical hemostats as Class II? Hearing no comments, I will assume that the panel is comfortable with the proposal that these topical hemostats both with and without licensed thrombin be classified as Class II medical devices. Is that sufficient, Dr. Dean?

Dr. Dean: Yes, thank you very much, Dr. Harris and the panel for your input on the classification.

Dr. Harris: Great. At this time, before we conclude, I would like to ask our representatives Ms. Brummert, our consumer representative, Dr. P. LaMont Bryant, our industry representative and Ms. Melissa Fisher our patient representative if they have any additional comments beginning with Ms. Brummert.

Ms. Brummert: No additional comments.

Dr. Harris: Thank you. Dr. Bryant?

Dr. Bryant: Just on behalf of the industry, we would like to thank the FDA and their team for the diligent work and the panel for your commitment to patients.

Dr. Harris: Thank you. Ms. Fisher.

Ms. Fisher: No, I don't. But I would like to thank the panel for including patient representative for this very important process. We really appreciate being part of it. Thank you.

Dr. Harris: Thank you. So at this time, the panel will hear summations and/or comments or clarifications from FDA. Dr. Dean, not that I would seek to limit you, but I'm told you have ten minutes.

Dr. Dean: I believe Dr. Krause is planning to do the summation for the day. Thank you.

Dr. Harris: Dr. Krause.

Dr. Krause: Thank you. For the FDA, I would like to thank our chairperson Dr. Harris, our patient, industry, consumer, and other representatives, our expert panel members for their discussion and recommendations regarding tissue expanders, mammary sizers, wound dressings with animal derived components, polymer wound dressings, and topical hemostatic wound dressings, and for all the good discussion and all the great information we received from you today. Thank you and have a good evening.

Dr. Harris: Thank you, Dr. Krause. So I'd also like to thank the panel members, FDA, and all of the Open Public Hearing speakers for their contributions for today's panel meeting.

This meeting is now adjourned.