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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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GENERAL AND PLASTIC SURGERY DEVICES PANEL

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September 21, 2016
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, Maryland

PANEL MEMBERS:

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MURAD ALAM, M.D.	Panel Member
KELLY HUNT, M.D., FACS	Panel Member
KAREN BURKE, M.D., Ph.D.	Panel Member
MICHAEL MILLER, M.D., FACS	Panel Member
GREG CAMPBELL, Ph.D.	Panel Member
JAMES HOLMES IV, M.D., FACS	Panel Member
FLURYANNE LEACH, M.S., RN	Panel Member
L. BARTH RELLER, M.D., FACP	Panel Member
WILLIAM HICKERSON, M.D., FACS	Panel Member
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GEETIKA SOOD, M.D.	Panel Member
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MICHELLE LOTT, RAC	Industry Representative
JO-ELLEN DE LUCA	Patient Representative
YUSEF SAYEED, M.D., M.P.H., M.Eng., CPH, CMRO, CME, COHC, EIT	Consumer Representative
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M E E T I N G

(8:00 a.m.)

DR. HARRIS: Good morning, it's 8 o'clock. I'd like to call the meeting of the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee to order.

I'm Dr. Hobart Harris. I'm the Chair of the Panel. I am a Professor of Surgery at the University of California, San Francisco.

I note for the record that the Panel members present constitute a quorum as required by 21 C.F.R. 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 regarding the classification of certain pre-amendment wound care products containing antimicrobials and other drugs that are regulated under product code FRO, Dressing, Wound, Drug. FDA is seeking Committee input on the indications for use, risks to health, and safety and effectiveness of these wound care products and how they should be classified.

Before we begin, I'd like to ask our distinguished Panel members and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation. And we begin here to my right.

MS. LOTT: Michelle Lott, Lean RAQA Systems. My area of expertise is regulatory and quality system strategy. I'm the Industry Representative on the Panel.

DR. SAYEED: Dr. Yusef Sayeed, the Consumer Representative. My primary specialty is occupational medicine. I'm currently in an interventional pain fellowship at the Deuk Spine Institute. I also have master's degrees in both engineering and public health. My area of expertise is musculoskeletal injury and musculoskeletal ultrasound.

MS. DE LUCA: Jo-Ellen De Luca. I am a retired reading specialist and the Patient Representative here. I'm the founder and organizer of about 2,500-plus members of Colon

Cancer Solutions, an online support group for people with colon cancer and don't know what to do. And it's my pleasure to be here. Thank you.

DR. CAMPBELL: Hi. I'm Greg Campbell, and my area of expertise is biostatistics. For 20 years I was the Director of the Division of Biostatistics in the Center for Devices and Radiological Health until I retired last year. I'm now an independent consultant with GCStat Consulting. Thanks.

DR. HOLMES: Good morning. I'm Jimmy Holmes. I'm an Associate Professor of Surgery at Wake Forest University School of Medicine and the Director of the Burn Center at Wake Forest Baptist Medical Center in Winston-Salem, North Carolina.

DR. ELMORE: I'm Susan Elmore, a veterinarian toxicologic pathologist at the National Toxicology Program and the National Institute of Environmental Health Sciences. And one of my areas of expertise is in the design, conduct, and evaluation of animal studies.

DR. HICKERSON: I'm Bill Hickerson. I'm Professor of Plastic Surgery at the University of Tennessee, and the Director of Firefighters Regional Burn Center at Regional One Hospital.

DR. BURKE: I'm Dr. Karen Burke. I am a dermatologist in private practice, and I'm on the faculty of Mount Sinai Medical Center in New York.

DR. ALAM: I'm Murad Alam. I am Vice Chair and Professor of Dermatology at Northwestern University. I do clinical dermatology and clinical trials.

MS. WASHINGTON: My name is Evella Washington. I'm the DFO.

DR. HUNT: Kelly Hunt. I'm Professor of Surgery at the MD Anderson Cancer Center in Houston, Texas, and Chair of the Department of Breast Surgical Oncology.

DR. MILLER: Michael Miller. I'm Professor of Plastic Surgery and the Chair of the Department of Plastic Surgery at the Ohio State University.

MS. LEACH: I'm Fluryanne Leach. I am an infection prevention and control

practitioner, recently retired from Walter Reed National Military Medical Center.

DR. RELLER: Barth Reller. Infectious diseases, medical microbiology, Professor of Medicine and Pathology, Duke University.

DR. PATEL: Jean Patel. I'm from the Centers for Disease Control and Prevention in the Division of Healthcare Quality Promotion. My expertise is in antimicrobial resistance detection and surveillance.

DR. SOOD: Hi, I'm Geeta Sood. I'm an Assistant Professor at Johns Hopkins University and the hospital epidemiologist at Johns Hopkins Bayview, and my expertise is infectious diseases.

DR. ASHAR: Good morning. My name is Binita Ashar. I am a general surgeon, and I'm the Director of the Division of Surgical Devices at the Center for Devices and Radiological Health.

DR. SHERMAN: Good morning. I'm Rachel Sherman. I'm an internist of special infectious diseases, and I'm the Associate Deputy Commissioner from Medical Products and Tobacco, substituting for Dr. Califf.

DR. HARRIS: Thank you.

Members of the audience, if you have not already done so, please sign the attendance sheets that are at the tables by the doors.

Ms. Evella Washington, who is the Designated Federal Officer for the General and Plastic Surgery Devices Panel, will now make some introductory remarks.

MS. WASHINGTON: The Food and Drug Administration is convening today's meeting of the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act 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. Section 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. Section 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 financial conflict of interest.

Related to the discussions 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 to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 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, the Panel will discuss and make recommendations regarding the classification of certain wound care products containing antimicrobials and other drugs as part of the routine process for device classification. These products are regulated under product code FRO, Dressing, Wound, Drug, and are considered pre-amendments because they were in commercial distribution prior to May the 28th, 1976, when the Medical Devices Amendments were enacted, and have not yet been classified under Section 513 of the Federal Food, Drug, and Cosmetic Act.

As a part of the classification process, FDA is seeking Panel input on the indications for use, risks to health, and safety and effectiveness of these wound care products, and how

they should be classified. They may be classified in Class I (general controls), Class II (special and general controls), or Class III (premarket approval (PMA), requiring demonstration of safety and effectiveness for each product).

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208.

Michelle Lott is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Lean RAQA Systems, LLC.

We would like to remind members and consultants that if the discussions involve 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 their 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 at the registration table during this meeting and will be included as a part of the official transcript.

Thank you.

For the duration of the General and Plastic Surgery Devices Panel on September the 21st, 2016, Dr. Susan Elmore has been appointed to serve as a Temporary Non-Voting Member, and Ms. Jo-Ellen De Luca has been appointed to serve as a Temporary Non-Voting Patient Representative. For the record, Ms. De Luca serves as consultant to the Gastrointestinal Drugs Advisory Committee at the Center for Drug Evaluation and Research, and Dr. Elmore serves as a consultant to the Psychopharmacologic Drugs Advisory Committee at CDER. These individuals are special Government employees who have undergone the customary conflict of interest review and have reviewed the material to be

considered at this meeting.

These appointments were authorized by Dr. Janice Soreth, Acting Associate Commissioner for Special Medical Programs, on September the 19th of 2016.

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

The transcript for today's meeting will be available from Free State Court Reporting, Incorporated.

Information on purchasing videos of today's meeting can be found on the table outside the meeting room.

Handouts of today's presentations are available at the registration desk.

And the press contact for today's meeting is Fallon Smith.

I would like to remind everyone that members of the public and the press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until after the Panel meeting has concluded.

If you would like to present during today's open public hearing session, please register with Ms. AnnMarie Williams at the registration desk.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time that you speak.

Finally, please silence your cell phones and other electronic devices at this time.

Dr. Harris.

DR. HARRIS: Thank you.

We will now have a summary of Day 1 by Dr. Cynthia Chang, along with clarifying questions from the Panel.

Dr. Chang.

DR. CHANG: Good morning, everyone, and welcome to the second day of our

classification panel meeting for wound dressings combined with drugs.

Yesterday's discussion focused on the clinical use, guidelines, benefits, risks, and evidence related to these products. To focus the deliberations, the FDA presenters first explained the historical and current regulation of these products, including the testing and evaluation currently provided.

Additionally, FDA outlined the clinical considerations for these products from premarket and postmarket perspectives, and we reviewed the benefits and risks for antimicrobial agents in wound dressings, especially in light of antimicrobial resistance concerns.

From a slightly different global perspective, we heard from Professor Finn Gottrup regarding the international challenges in the area of wound care.

During the afternoon deliberations, the Advisory Committee provided insightful comments on the diverse range of clinical and scientific issues. I would like to highlight some of the themes that kept coming up, which may be helpful to consider when recommending classification of these products today.

First, we presented three subcategories for the wound dressings with drugs based on their physical form, and from the discussion, it seems the Panel agrees that this is a reasonable method for grouping the products. If there are more appropriate ways to categorize or further subcategorize these products as you consider the groupings by benefit and risk, please provide these recommendations.

There was also discussion about the clinical relevance of specific claims regarding the barrier function of the dressing and claims of reducing bioburden on the dressing itself. The Committee indicated that there would be a benefit to improved vernacular or communication regarding terminology and claims applied to wound dressings and antimicrobial agents. As you create categories of products, you may consider how the

claims, such as those discussed yesterday afternoon, should fit within the category you are creating or whether there are certain claims that should be excluded from certain categories.

You noted the diversity of wound types and patient conditions and discussed how the indications may vary among or within the three subcategories of dressings. As you discussed the types of evidence needed to support various claims, whether bench, animal, or clinical data, you suggested assessments of such patient-reported outcomes, registries, and real-world evidence since wound dressings with drugs are only part of the overall wound care received by a patient.

There was concern regarding the risks and potential mitigations posed by the inclusion of more than one antimicrobial in a single product, and how to assess the effects of the various ingredients in these situations where the effect may be synergistic, additive, or antagonistic with respect to reduced bioburden and possibly promotion of resistance.

Going forward today, please continue to remember the diversity of products, ingredients, wounds, and patient conditions as you comment on the risks to health posed by wound dressings combined with drugs.

As mentioned yesterday, FDA does not believe it is appropriate to classify these products as Class I, considering the possible permutations of drug concentrations and combinations, because general controls alone are insufficient to mitigate the risks.

Similarly, for these risks, please think about how specific types of testing or controls, whether bench, animal, or clinical, might be able to fully address the risks. There may be specific claims, intended uses, technological characteristics, or drug types that may pose more or less risks than others, and some may be feasible to address with special controls and some may not. When considering this, please remember the variety of ingredients present in cleared products in this category, including:

- Active ingredients in approved or monograph drugs;
- Chemicals that may be identified as inactive ingredients in approved drug products;
- Other chemicals with antimicrobial activity;
- Plant-derived materials and botanical extracts; and
- Other additive components, including salts, surfactants, and thickening agents.

Please also note that the conditions of use and indications for use vary from the drug approvals and monographs.

Additionally, please also consider the roles of the different categories of antimicrobials primarily included in dressings: the metals, biguanides, quaternary ammonium compounds, and oxidizing agents, as well as more targeted antimicrobials such as antibiotics.

We look forward to hearing your thoughts on this complex product area and what FDA should consider in our classification process.

Thank you.

DR. HARRIS: Thank you, Dr. Chang.

Ms. Angela DeMarco, who is on detail -- I'm sorry. Yes, Ms. Angela DeMarco, who is on detail in the Premarket Notification (510(k)) Program Office at the FDA will be providing a classification overview to the Panel.

I'd also like to remind 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.

Ms. DeMarco.

MS. DeMARCO: Thank you. Good morning. I'm going to be discussing device

classification.

So the purpose of this Panel meeting is to discuss the indications for use, risks to health, and safety and effectiveness of wound dressings combined with drugs, currently a pre-amendment, unclassified device type with product code FRO. You will also provide input to FDA on the classification of wound dressings combined with drugs into either Class III, Class II, or Class I.

So a pre-amendment device is a device of a type that was introduced into interstate commerce prior to May 28th, 1976, which is the enactment date of the Medical Device Amendments.

An unclassified device is a pre-amendments device that was not classified by the original classification panels. Therefore, no classification regulation currently exists for this device type.

Pre-amendment devices are classified after FDA has received a recommendation from a device classification panel, published the panel's recommendation for comment along with a proposed rule classifying the device, and published a final rule classifying the device.

There are three device classes: Class I, Class II, and Class III. Class I devices are subject to general controls and are considered low to moderate risk. Class II devices are subject to general and special controls and are considered moderate to high risk. Class III devices are subject to general controls and premarket approval, or PMA, and are considered high risk. Devices are classified based on the controls necessary. A device should be placed in the lowest class whose level of control provides reasonable assurance of safety and effectiveness.

Class I devices are devices for which general controls are sufficient to provide reasonable assurance of the safety and effectiveness, and they typically do not require

premarket review by the FDA prior to being marketed.

General controls include:

- Prohibition against adulterated or misbranded devices;
- Good manufacturing practices;
- Registration of manufacturing facilities;
- Listing of device types;
- Recordkeeping, etc.

Some examples of Class I devices include general surgical instruments, surgical gloves, and medical adhesive tape.

Class I devices are devices which cannot be classified into Class III because they are not life sustaining, life supporting, of substantial importance in preventing impairment of public health, and because they do not present a potential unreasonable risk of illness or injury. They are also devices which 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 cannot be classified into Class I because general controls are insufficient to provide reasonable assurance of the safety and effectiveness of such a device, and for which there is sufficient information to establish special controls to provide such assurance. Class II devices typically require premarket notification, or a 510(k), prior to being marketed.

Special controls include:

- Performance standards;
- Postmarket surveillance;
- Patient registries;
- Special labeling requirements; and

- Development and dissemination of guidelines.

So how are special controls used? As an example, tissue adhesive for the topical approximation of skin devices were reclassified from Class III to Class II with special controls. FDA issued a special controls guidance to mitigate the risks to health. These special controls include:

- Biocompatibility testing
- Material characterization
- Chemistry
- Bench testing
- Sterility
- Labeling
- Animal and Clinical testing

These special controls, in combination with the general controls, provide reasonable assurance of safety and effectiveness. Companies must provide evidence in their 510(k) submissions of how the special controls were addressed.

Some examples of Class II devices include surgical sutures, fetal heart monitors, gastrointestinal feeding tubes, and hemodialysis systems.

Class III devices cannot be classified into Class II because insufficient information exists to determine that general and specials controls are sufficient to provide reasonable assurance of safety and effectiveness, and the devices are life sustaining and/or life supporting, or of substantial importance in preventing impairment of human health, or presents a potential unreasonable risk of illness or injury. Class III devices typically require premarket approval, or PMA, prior to being marketed.

Some examples of Class III devices include breast implants, obesity treatment devices, and implanted urinary and fecal incontinence devices.

This chart is a visual representation of the information provided. As you move down the flowchart, you determine which class the device belongs in. So if general controls are sufficient, the device is Class I. If they're not sufficient, you ask whether or not there is sufficient information for special controls. If so, the device is classified into Class II. If not, you move further down the flowchart and ask whether or not the device is life supporting/sustaining or substantially important to human health. If so, the device is classified into Class III. If not, you ask whether or not there is a potential unreasonable risk. If so, the device is classified into Class III. If not, the device is classified into Class I.

Reasonable assurance of safety and effectiveness is defined in 21 C.F.R. 860.7(d)(1). It states that "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 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 a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended use and conditions of use."

Reasonable assurance of effectiveness is defined in 21 C.F.R. 860.7(e)(1). It states that "There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended use and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results."

Valid scientific evidence is defined in 21 C.F.R. 860.7(c)(2) and includes well-controlled investigations, partially controlled studies, studies without matched controls, well-documented case histories, and reports of significant human experience with a

marketed device from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use.

So what do we need from the Panel today? You need to review and discuss available scientific evidence regarding safety and effectiveness of wound dressings combined with drugs. We need input on classification of the device, whether or not it will be classified into Class III, Class II, or Class I. And the input and recommendations should identify risks to health presented by the device; whether the device is life supporting or life sustaining, of substantial importance in preventing impairment to human health, or presents a potential unreasonable risk of illness or injury; whether sufficient information exists to develop special controls; and if so, identify those special controls that provide reasonable assurance of safety and effectiveness; and determine whether general controls alone are sufficient.

So what will happen after this Panel meeting today? FDA will consider the available evidence, including the input of this Panel and the public comments. FDA will issue a proposed rule, proposing classification of the device and seeking public comment on the proposal. FDA will issue a final rule identifying the appropriate class. If Class I or Class II, the devices may continue to be marketed. If Class III, FDA will issue a separate call for PMAs. Existing devices will remain on the market until submission of a PMA by a specified time to continue marketing. And if a PMA is not approved, devices will be considered misbranded and must be removed from distribution.

Thank you.

DR. HARRIS: Thank you. I'd like to thank the FDA's representatives for their presentations. We'll now have brief clarifying questions from the Panel. Please remember that the Panel may also ask -- well, there are no sponsors, so they'll just have some questions.

So Dr. Alam.

DR. ALAM: Hi. Murad Alam. Thank you for that presentation. I just have a couple of questions for clarification. In your discussion you give some examples of Class II devices, and those included surgical sutures. So Question 1 is -- could you discuss why -- surgical sutures seems like a pretty good proxy for the sort of products we're discussing today to the extent that it's placed in wounds and so forth. Could you discuss the logic behind that in the context of the products we're looking at?

And the other question pertains to the flowchart for classification that you included in this talk. If you follow the flowchart down, there is a case where general controls were found to be insufficient. Sufficient information for special controls was not available. Life supporting/sustaining, substantially important to human health was determined to be no, and potential unreasonable risk was determined to be no, and then it kind of goes back to Class I. Are you familiar with any products that have actually gone through all of that pathway and then been reclassified as Class I at the end of that determination?

Thank you.

MS. DeMARCO: To answer your first question --

(Off microphone comment.)

MS. DeMARCO: Oh, you want to answer one? Okay.

DR. CHANG: So I think I can handle the first question on surgical sutures, and the question, I believe, was why surgical sutures would be considered appropriate for Class II; is that correct? So --

DR. ALAM: And if there are any considerations that would sort of make you think of surgical sutures in a different way than the products we're looking at, at present.

DR. CHANG: Okay. So this is Cynthia Chang.

So for surgical sutures, I believe there are a number of special controls that are

considered in the premarket review of those sutures. They can be considered implanted devices. In some cases, some of them are degradable. And so there is a considerable amount of information that's required regarding the material characterization and biocompatibility of those devices, including animal testing as well as mechanical testing of how long the sutures are able to maintain their mechanical strength in vivo, up to a certain time as demonstrated by animal studies. In addition, there are specific mechanical and physical characterization tests that are required for various types of sutures. And I think that is some of the considerations that may be similar to wound dressings.

Does that answer the question?

DR. ALAM: Yes.

DR. SHERMAN: But you just want to remember that sutures are one product, and we're looking at a combination product, a device and a drug.

MS. KRUEGER: I'm going to answer the question regarding the flowchart, which is an interesting question, and I understand why it causes confusion. This is the way that the statute is crafted in our laws. You asked really for a specific example, and we have not classified a product using that final prong, going back to Class I. So we don't have any examples, and we haven't used that or operationalized that as a form of classification at this point.

DR. ALAM: Thank you.

DR. HARRIS: Dr. Sayeed.

DR. SAYEED: Yusef Sayeed, Consumer Representative.

So I have a couple of general questions that I asked yesterday. I'm going to re-ask them today because today is the classification day. And so specifically, when discussing Class II products, we're talking about some of the controls that we could use. What assurance can the FDA give the Panel that the controls will be a substantial impact in terms

of labeling, in terms of doctors using the labeling, in terms of manufacturers following appropriate documentation? This is a big concern to consumer groups across the country, not just on these devices but devices that come to this Panel and almost every panel meeting.

And then the second question that I'd like to ask the FDA is in terms of Class II post-surveillance studies, what reassurances can you give the Panel today that if we were to recommend a Class II device for these overall devices, that the appropriate post-surveillance studies will take place within a timely manner?

Thank you.

MS. KRUEGER: This is Angela Krueger. I'll address that question.

So your first question was regarding assurance related to special controls and whether they should be put in place for certain categories of products that we're discussing today, how we would ensure that they are followed.

So special controls are requirements. They are essentially a recalibration and a baseline for all of the products that we would put into a specific category where special controls are put into place. All companies must meet those special controls. What we have generally required is through the 510(k), when they're submitted, for them to actually demonstrate how they meet all of the special controls that are outlined in the regulations, but we do that from a premarket perspective. As was mentioned from Ms. DeMarco, they're also subject to general controls as well. So that would be the way that we address the issues from a premarket perspective.

Your second question was related to postmarket surveillance, and that's also a good question. We can utilize postmarket surveillance as a special control, and we have done that in several cases for products that we have put through our de novo classification and put them into Class II. So we can utilize postmarket surveillance as a special control, and

then the same requirements would apply in terms of how we evaluate that. They need to meet that special control, and we would assure that they meet that special control.

DR. SHERMAN: Dr. Harris, could I just make one last --

DR. HARRIS: Yes.

DR. SHERMAN: Rachel Sherman, FDA.

So my background is drugs, so my colleagues at CDRH have been assiduously trying to tutor me on this, but it's, at least for me, hard to wrap my mind around it. Since we're talking about two components, our controls have to be adequate, if that's the right word, for both components. And it's important to remember something that came up yesterday. And we have two colleagues from our Office of Chief Counsel here, our lawyers who can help talk about this, if we need. Some of these drugs will have been approved under the drug standard, but some of them will be unapproved drugs under the drug standard. So those are some complications or subtleties to keep in mind as we consider the special controls. I think CDRH has -- our colleagues have very nicely suggested Class I is not appropriate, so we really are talking about special controls or beyond.

DR. HARRIS: You had a follow-on question?

DR. SAYEED: So just to follow up on my second question. When we're talking about post-surveillance studies, what type of time frame are we talking about, because that has been the question. You know, the GAO report came out last year. That discusses only 20% of medical devices are studied in postmarket studies over an 8-year period. And so that's a big concern for the people that I represent and the American people. If we vote for a Class II product today, are they going to be studied?

MS. KRUEGER: This is Angela Krueger again.

Regarding postmarket studies, so I think what we're talking about and what would be helpful for our -- for the input from the Panel today is to understand if you believe that

postmarket studies are, as a total package, part of a special control which would provide a reasonable assurance of safety and effectiveness for certain devices that are being discussed today. That would be helpful to know. If we were to build that into a special control as part of the classification and make that a requirement, at the point at which the final rule goes out, those would be requirements. Products that are put into that category would be subjected to them, and we would ensure that they are followed.

DR. HARRIS: Dr. Sood. Oh.

DR. ASHAR: I just wanted to add that, you know, postmarket studies are very helpful to us to monitor adverse events and to assess a device in ways that we wouldn't be able to otherwise in a premarket. However, it is intended to be in lieu of understanding the benefit/risk profile in the premarket. The level of evidence necessary for all of our premarket reviews is reasonable assurance of safety and effectiveness. And so I just don't want the Panel to misinterpret postmarket studies as being tabling of issues to assess later.

DR. HARRIS: Dr. Sood.

DR. SOOD: Thank you. I have a quick question. Thank you for the presentation.

It's very helpful to understand, as we're trying to figure out the risk of these products, to see what the compare groups are, what other products are that are in the Class I, Class II, and Class III. You had mentioned, for Class I, that there are surgical instruments that are considered Class I. Can you talk a little bit more about some of those examples?

DR. CHANG: So I believe one of the examples was surgical instruments. Those could include manual surgical instruments such as scalpels, and for those, I believe that the idea in placing them in Class I at the time was that their intended use was generally known and that general controls such as quality systems or good manufacturing practices such as sterility and basic material manufacturing requirements were adequate for assuring a

reasonable assurance of safety and effectiveness.

DR. SOOD: Thank you.

DR. HARRIS: Ms. Lott.

MS. LOTT: I've got two follow-up questions from yesterday, if we can go back a little bit. One is for Dr. Gottrup. I read your paper last night on the recommendations for industry on how to potentially -- some alternatives for structuring trials and whatnot. In that process, did you come up with any recommendations to the regulators? Or if you have not, have you had any traction with the regulators, be it the competent authorities in Denmark or the European Commission, on kind of indoctrinating some of your research and conclusions about wound care?

DR. GOTTRUP: I can say that we have had no contact, in this time, with the regulators. So I can't give you an answer on that, at that moment, yeah.

MS. LOTT: At this point, based on the research you've done so far, if you did get the opportunity to make some recommendations to the European Commission on this matter, from a regulatory perspective, what would you encourage them to do as regulators?

DR. GOTTRUP: I must say that I am not quite sure what I would do because it's part -- the group, we were making this paper, was split up like you are here, different type of people, and I am not the correct one to do it because I am a clinician.

MS. LOTT: Right.

DR. GOTTRUP: That way. So one of the other ones, if you sent me an answer to that, I can give you the name who can give you the exact, what should I say, answer on that because I'm not the correct one to do that at that moment. I have some ideas, but I'll prefer to --

MS. LOTT: Right.

DR. GOTTRUP: -- do the right thing in the right time.

MS. LOTT: Yeah. And in Europe, you do have alternates with postmarket surveillance, postmarket --

DR. GOTTRUP: Yeah.

MS. LOTT: -- clinical follow-up that were also addressed in your paper that aren't commonplace here.

DR. GOTTRUP: Absolutely, yeah.

MS. LOTT: Yeah, okay.

DR. GOTTRUP: Okay.

MS. LOTT: And then the other question that I wanted to follow up on was a comment made by Dr. Alpert yesterday during her talk and that was mentioning real-world data. Dr. Chang also brought it up this morning. I know this question is for the FDA. I know the FDA, in the last month or two, has published a guidance document on real-world data. Can you speak at all to how manufacturers might utilize that guidance document in the outcomes of this process, this classification process, and potential clinical trials and data that we're evaluating here?

DR. ASHAR: Sure, I'll try to address that as best I can, and others from FDA can chime in. We're very excited about the prospect of having registries that collect real-world data where we think that they're using cleared products to capture how a clinician might seek to care for their patient and understanding even better some of the outcomes associated with that care. We understand, as physicians seek to care for their patient, that they may use these devices in novel ways. So we don't want that information to be lost, so we're hoping that these registries can capture that information, as well, so that some of that experience can be understood and potentially become on label. So it can be used for multiple purposes. This real-world data can be used for surveillance, for assessing long-term adverse events, for understanding new uses that potentially can become on label.

Hopefully that addresses it. If others from FDA have additional thoughts, please add them.

DR. HARRIS: Dr. Campbell.

DR. CAMPBELL: So I could add a little to that, only because I'm going to give a talk at a statistics meeting next week on this topic, and one of the ideas is that -- and the guidance talks about this, the use of expanded indications. So if you have a device that's approved for one indication, you might use real-world evidence to gain information to expand the indication. And the other one that comes to mind is something Dr. Califf mentioned yesterday. If you want to have a really high-quality registry, you could do a randomized trial within the registry. So those were points, I think, that the guidance did mention.

DR. HARRIS: Dr. Alam.

DR. ALAM: I just wanted to ask a follow-up about the suture question I'd asked earlier. I was looking it up, and I just want to make sure I'm understanding correctly. It seems that coated Vicryl, which is Vicryl with antibacterial, was approved through the 510(k) process in 2014. Would that mean that -- is that considered to be a combination product because it has an antibacterial with suture? And would the 510(k) process represent a Class II approval? And if the answer is yes, is that typical for other sutures with antibacterials?

Thank you.

DR. ASHAR: I know that there are a couple of -- some sutures that we are regulating as Class II that are combination products. While the majority are not, there are some. For example, there's a triclosan suture that is regulated as Class II. I'm not sure of the suture that you're speaking of, that you cited.

DR. ALAM: Thank you.

DR. HARRIS: I had a question for either of the FDA representatives. If you are dealing with a product that you feel is substantially important to human health but has

overall moderate to low risk, could a manufacturer's claim require you to actually pursue PMA or clinical testing? In other words, if I'm saying that this product is going to actually influence the behavior or physiology of the wound, even though it's going to be a low-risk product, does that automatically require clinical testing?

MS. KRUEGER: This is Angela Krueger, CDRH.

You raise an important point, and I think that we are looking to the Panel to help us cull out specific information about claims. I think when we're looking at the definitions and practically putting things into specific classes, I think we have to keep in mind and focus on our discussion today regarding whether or not there's sufficient information to put something into Class III or Class II, so sufficient information to develop special controls and establish special controls to provide that reasonable assurance of safety and effectiveness. I think what you're getting at is really how do you manage the benefit/risk as a combination, and how do you create that balance? And so I think that, for specific claims, if you don't find that there is sufficient evidence to create special controls to provide that reasonable assurance of safety and effectiveness, that's what we would like to understand from the Panel today.

DR. SHERMAN: Could I just expand on that slightly? Rachel Sherman.

So just arguably, if the wound dressing, combination wound dressing were to make -- the manufacturing claimed treatment, treat this infection, treat an infected wound, then we'd have to make two decisions: (1) which component would we think had the primary mode of action, the antimicrobial or the dressing? And then it would be bumped into the evidentiary standard of either a device or a drug. So it could be then bumped into the drug standard 505, which would be substantial evidence. But my CDRH colleagues will correct me if I'm wrong. In the device standard, it would be more than reasonable assurance of safety and effectiveness; is that correct?

DR. ASHAR: Yes, that's right. And I just wanted to break it down even further. Say that we're reviewing these as Class II 510(k) products. With each and every review, the first question that we're asking is whether the product has the same intended use and the same indications for use as the predicate device. So if the predicate device didn't have treatment claims in it, then that would automatically cause questions to be asked as to whether this is appropriate for 510(k) review.

DR. HARRIS: Dr. Hickerson.

DR. HICKERSON: It seems if you had a registry of these devices, that if something came up down the road that looked as if it were treating something, then you'd be able to go back and pull that out of the registry to get those extra claims in that manner as well. So it seems as if, along those lines, that that could be very beneficial and something that we don't have today. The other thing would be that it seems like that we're always trying to break everything down into its parts, which sounds great. But sometimes when you have an additive aspect, it's not the sum of those two parts. So I would foresee how that could be very difficult when you set that as your absolute standard going forward as well. For example, botanicals and things like that combined could give you a big headache if you're trying to break it down into individual parts rather than seeing the whole.

DR. SAYEED: I guess I have a general question for the FDA, also, in terms of public health. So, you know, we're talking about antibiotic resistance, and even though these products are low-risk products individually, it seems like a high-risk societal issue. So, you know, in terms of the level of evidence that's required, if you didn't have any evidence for a product, you would probably classify it as a Class III if there just isn't a lot of evidence; is that correct?

MS. KRUEGER: I think that we have to look at the definitions and the product type as a whole. I think what we will be asking the Panel today is to look at specific elements that

help us put things into categories or classes of products. And so one of those things that we will ask the Panel to look at is risks to health, and I think what you're getting at regarding the societal risk is how do you balance that risk with a specific benefit. I do think that the Panel needs to help us understand what that benefit/risk profile looks like for these classes of products so that we are best able to put them into the appropriate class based on the definitions in the statute.

DR. SHERMAN: Just to add to that, the one place we've actually written about societal versus individual risk is in the expanded access regulation, and in there -- because we're always trying to balance societal risk and individual risk or societal benefit and individual benefit -- there, we talk about I don't want to say competing, but sometimes differing pressures. And, for example, if an expanding access program is felt to be making completion of the development program impossible or difficult, then the expanded access program will be terminated because the Agency's position is the most equitable and the best thing for society is informed marketing. So that's one place we've talked about it.

DR. HARRIS: Dr. Miller.

DR. MILLER: This is Mike Miller.

This whole thing is a little confusing because I think it's difficult to separate out what exactly we're trying to accomplish in terms of understanding these devices. I think we need help from the FDA to understand what do you want for these devices. I mean, if we want to have devices that enhance wound healing or prevent infection, that's a whole issue in itself. If we expect the devices to demonstrate that, then that's going to require some work, maybe Class III. I don't know.

But if we're separating the two, then this is almost analogous to having dressings with pigments added to change the color. You know, do we want pink dressings or do we want blue dressings? We have to put a pigment in. We have to go through all the

approvals to prove the pigments are dangerous or whatever. But the endpoint is does the pigment make the dressing pink or does it make it blue? So okay, we can draw a conclusion on that, that's pretty safe, and this is analogous to that because we're skirting the question of does adding the agent help the clinical outcome of a healed wound or a non-infected wound. We're not even looking at that. We're just saying does it prevent bacteria from growing in the dressing, regardless of whether it helps the wound or not. Well, to me, that's like asking about does the pigment change the color. Well, yeah, it does. So they're such different questions it's hard to know how to proceed with this classification issue, you know.

MS. KRUEGER: This is Angela Krueger.

This is a helpful discussion, and it actually sounds like there are members of the Panel who would like to respond to what you're saying, and I think what may be helpful is for us to kind of move past -- if there are specific classification discussion questions, you know, to talk about them here and then move into later portions of the agenda. What I would say related to your question is we have to look at a couple of things as part of this discussion, and one is we're classifying a product type as a whole. We're looking at them collectively. We are trying to bucket them appropriately because we understand there are a lot of products in this area. But we're also looking at the claims and intended uses that have been cleared and what the products are used for.

There was a lot of discussion yesterday afternoon regarding those claims and whether or not the Panel found them to be appropriate, and I think we'll consider that in classification decisions. But we also do need to come back to the products that are on the market, what they're intended for and whether or not there is evidence of what that benefit/risk profile is, and then appropriately bucketing them. I understand the challenges associated with, you know, how to do that in the context of the clinical setting, but that's

essentially what I think we need to try to walk through today as we look at the regulatory definitions and figure out where to put appropriate products, and we're really looking to the Panel for their recommendations on those particular issues.

DR. HARRIS: Ms. Lott.

MS. LOTT: I think Dr. Miller brings up a good point, and you addressed this yesterday as well, and the FDA yesterday reminded us, three or four different people about three of four different times, that we're specifically addressing management of the wound environment and we're specifically addressing the dressing, addressing the dressing -- sorry, that's a bit confusing -- not does the dressing treat the wound. And to your point, those are two totally different things, and I think it's going to keep our conversation much more efficient, as we make comments, to know which bucket we are commenting towards. And I think that that's going to make our classification discussions more productive and get us the right type of controls for those different sets of claims.

DR. SHERMAN: Just to expand on that, we're not either endorsing or contending for, one, a better word, the concept of wound management. We're presenting to you our conundrum. These products, over 700 of them, are on the market for these claims. This is a paradigm. I wouldn't say we inherited it. It was a deliberate decision on the part of the U.S. Congress in 1976 that these would be grandfathered in until we classified them. So my attorney friends, correct me if I'm wrong, so we are asking you in sense to split the baby a little bit. There was a lot of discussion about the importance of healing, and I don't think anyone would debate that. We were trying to pull out yesterday, and it's tricky, is there a benefit?

I think, Dr. Miller, you talked a lot about smell, which is very important. And we talked about if there's a lot of benefit, we'll take a lot of risk, and we've written about that in our regulations. And if there's very little benefit, we're going to tolerate very little risk.

So we are asking you to look at that gray area because, intuitively, one thinks about, well, pink could be very important if you're a parent and you want to put the bandage on your kid, but you would not accept a toxic pink. So we are asking you to -- and it's impossible to completely split them apart because in the end of the day, we're worried about or concerned about or approve or clear on the basis of whether there's a benefit.

MS. LOTT: Do you feel like it would be helpful for the other members of the Panel to explain the difference between an indication and a claim and how those things roll into FDA? Like it's indicated for management of the wound environment. My claim is that it does that by covering and protecting the wound. I don't know if that's relevant to these discussions, and I know most of the doctors wouldn't understand those elements of --

DR. ASHAR: I think for the purposes -- yeah, I think for the purposes of discussion, I think it might just be easier to consider them together rather than stratifying them. If you could just talk about an indication and what the benefit/risk profile is for that indication or claim together, and then how you would potentially classify that, that would be helpful to us. We would like this to be a scientific-based discussion to inform our regulatory process.

DR. HARRIS: Dr. Burke.

DR. BURKE: I just wanted to clarify that yesterday we were dealing with the dressings, and today we're dealing with the clinical use of those dressings and the clinical effect on the patient and the wound. I mean, from what I read, that seemed what we're addressing today.

DR. SHERMAN: It's an interesting question. I think we think it's impossible to ever separate out the dressing from the patient completely, but the claims themselves are claims about the dressing, and what we're asking you is this complicated question. As Ms. Lott pointed out, it's a claim about what happens to the dressing, and we're asking you to think about, given the products involved, what might be the impact on the patient and the impact

on society, and if there are risks, are those risks justified by -- you're correct, we don't really care what happens to the dressing, apart and aside from the fact that it's used on a person, if that helps.

DR. HARRIS: Okay. Well, we'll be able to continue some of this discussion later in the day. It's now 9 o'clock, and we will proceed with the Open Public Hearing portion of this meeting. Public attendees are given an opportunity to address the Panel to present data, information, or views relevant to the meeting agenda.

Ms. Washington will now read the Open Public Hearing Disclosure Process Statement.

MS. WASHINGTON: Both the Food and Drug Administration and the public 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, FDA believes that it is important to understand the context of the 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 today. 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 will not preclude you from speaking.

DR. HARRIS: For the record, we have received nine requests to speak for today's meeting. We ask that you speak clearly to allow the transcriptionist to provide an accurate transcription of the proceedings of this meeting. Each speaker has been allotted 5 minutes,

and the Panel appreciates that each speaker remains cognizant of their speaking time.

The first speaker is Angela Bunn.

MS. BUNN: Good morning. I'm Angela Bunn. I'm the Director of Regulatory Affairs for the Americas for Mölnlycke Health Care. Mölnlycke Health Care is also an active member of the Alliance of Wound Care Stakeholders and the Coalition of Wound Care Manufacturers.

So in light of yesterday's presentations, the comments, the discussions, and questions, we believe additional clarification around specific topics may assist the Panel as they move toward classification recommendation today.

One of the things that we feel is important to use appropriately and consistently is terminology in regards to antiseptics versus antibiotics. We had this discussion yesterday, and this is of particular importance when discussing again the risk levels and the potential levels of antimicrobial resistance in regards to these types of dressings.

It should also be noted that we are unaware of any dressings in the FRO category that contain antibiotics, the agents specifically implicated in antimicrobial resistance today.

We define antibiotics as molecules that inhibit specific bacterial protein functions and target growing organisms. In contrast, antiseptics are non-specific chemical reactants, and we are unaware of any evidence suggesting they contribute to antibiotic resistance. This is in line with the comments provided yesterday from Brandon Kitchel of FDA.

We also would like to highlight a limitation of the clinical practice guidelines referenced yesterday and their recommendations with regards to the use of antimicrobial dressings. Many of the guidelines presented yesterday did not evaluate or consider wound dressings of this type. Therefore, for some indications, the use of these dressings was not recommended within the guidelines. However, as pointed out by Panel members, the absence of good data does not mean bad data, just lack of data. A lack of recommendation

does not necessarily correlate with a recommendation against the use of these dressings in these situations, and we will be providing more detail on the focus of these guidelines and identify additional guidances that do recommend the use of antimicrobial dressings in specific clinical situations in our written comments to the Panel.

As the Panel moves forward in these discussions of classification, it is important that we would like to address some issues that are related to the actual determining of classification. So all of these types of devices, and we're speaking directly to the wound dressings in the FRO category, are intended for wound management, as we've just had an open discussion about. These devices are designed specifically to manage the environmental condition of the wound in order to allow the body's normal healing process to proceed on its own.

Some of the performance characteristics associated with wound management include the management of exudate, the maintenance of the wound healing environment, physical protection of the wound, bacterial barrier functions, reduction of microbial colonization in the dressing, amongst others. We firmly believe that each of these performance characteristics can be supported by bench testing, as we have done today.

Specific to bacterial barrier and microbial colonization, in vitro methods exist which simulate clinical use and are capable of demonstrating the ability of the dressing to prevent external contamination and reduce potential bioburden in the dressing. One obvious clinical benefit of the reduction of colonization in the dressing is that the dressing does not become a nidus for infection.

In addition to this obvious benefit to the patient, a reduction of colonization in the dressing has also been shown to minimize the risk of exposure of the healthcare providers to potential airborne bacteria during dressing changes. The coalition will be providing, and intends to provide, the published data and written comments that supports this statement.

In conclusion, after considering all information presented over the past 2 days at this meeting, there has been no evidence provided that these devices raise any issue of safety in regards to antimicrobial resistance, nor is the efficacy of these types of devices clinically insufficient. Therefore, it is our recommendation that the Panel consider all data presented during these discussions in regards to antimicrobial wound dressings and continue to have them under wound management regulated under the 510(k) premarket notification process.

As was shared with us earlier this morning, the regulatory pathway is appropriate in terms of risks, not life sustaining, not life supporting, and the safety and efficacy should be maintained as today. It is recommended that this group of products be identified as a Class II with very special controls, providing very specific guidance on requirements to industry.

Thank you.

DR. HARRIS: Thank you.

Our next speaker is Dyane Tower.

(No response.)

DR. HARRIS: Maybe she'll come later. Next, we'll move to Karen Ravitz.

MS. RAVITZ: Good morning. My name is Karen Ravitz. I am the Healthcare Policy Advisor for the Coalition of Wound Care Manufacturers, and I appreciate the opportunity to speak with you this morning.

The coalition represents leading manufacturers of wound care products used by patients for the treatment of wounds. Many of our members manufacture antimicrobial wound care products, which are the subject of these meetings.

Antimicrobial dressings are currently classified under the FRO product code category, and as we've already discussed, they include, but are not limited to, solid wound dressings; gels, creams, ointments; and liquid wound washes.

While our written comments will address these issues in detail, the coalition has six main points that we would like to make this morning.

First, the coalition believes that the 510(k) process has proven, over the past 40 years, to provide sufficient controls for these low-to-moderate-risk device types and that they should be classified as Class II medical devices since the risks are well understood and they are controlled.

Second, we agree with the FDA that there needs to be separation of the products that are contained in the FRO category; it is too broad. Wound dressings in the FRO category need to be a separate focus with separate controls. We recommend that they clearly be distinguished from the other products such as gels and washes and that each category have a guidance document regarding special controls to support the indications for use and claims for these medical devices.

Third, products in the FRO category are low to moderate risk in terms of safety. Given the long history of the use of many of the products that are in this category, the coalition believes that there is no evidence that they have significantly contributed to the problem of antibiotic resistance. The benefits of use outweigh their well-understood risks, and there are publications to support these conclusions, which we will provide in our written comments to support this claim.

Fourth, there is adequate evidence to demonstrate the safety and effectiveness of FRO products. These products have been on the market since before 1976, and while there might not be RCTs, the studies that do exist are aligned with the claims that the manufacturers have made for these products over the years, and we will be providing additional data on this point in our comments as well.

Fifth, yesterday there was discussion regarding endpoints. The coalition would like to reiterate a point that was made. Wound closure is not the appropriate endpoint for

evaluating these products. There are other meaningful endpoints that benefit patients that need to be considered. Dr. Marissa Carter noted many of them in her presentation yesterday.

And finally, as you move forward with classification, we urge the Panel to note that when the U.S. Wound Registry applied for a PCORI grant, PCORI rejected the proposal, stating that chronic non-healing wounds such as diabetic foot ulcers were not a national healthcare priority. We disagree. The U.S. Wound Registry currently has more than 150,000 patients with over 200,000 wounds. To Dr. Califf's point yesterday, the U.S. Wound Registry is able to create matched cohorts using validated wound healing index. We have the tools needed to harness registry data to answer other questions as well.

More than 52% of chronic wound care patients are prescribed systemic antibiotics, sometimes more than once, and nearly 10% are treated with topical antibiotics. Therefore, evaluating resistance or any other issue pertaining to the safety and effectiveness of wound dressings is exceedingly difficult given this patient population.

In summary, the coalition recommends that the antimicrobial wound dressings in this FRO category are low to moderate risk, have been in the marketplace for many years, and should be classified by the FDA into either Class I or II.

Thank you.

DR. HARRIS: Thank you.

Our next speaker will be Jonathan Hopper.

DR. HOPPER: Mr. Chairman, Panel members, ladies and gentlemen, good morning, and thank you for giving me the opportunity to present to you today. My name is Dr. Jon Hopper, and I'm speaking as a paid consultant on behalf of ConvaTec, who formerly employed me as their Vice President of Medical Affairs for North America. I trained as a trauma surgeon in the United Kingdom. I was a regulator at the MHRA for almost a decade,

and I've been in the wound industry -- of the medical devices industry for over 10 years, 7 of which have been with companies associated with wound-related technology.

My objective this morning is to review ConvaTec's written comment that was sent to the Agency; clarify the intended purpose, as others have, of antimicrobial dressings; review the safety and effectiveness of those dressings containing ionic silver; discuss the resistance concerns and propose the optimal regulatory pathway for this particular group of FRO devices.

As has been said many times, it's really important for the Panel to understand that the purpose of antimicrobial dressings are designed to manage wound exudate -- that's the primary purpose -- to optimize the environment for moist wound healing whilst acting as a barrier to protect the wound as it closes. In most wounds, this can be achieved without the addition of an antimicrobial agent such as ionic silver.

However, when managing infected wounds or wounds with a large bioburden or at-risk wounds that the treating clinician feels likely to be detrimental to wound closure, then the addition of ionic silver to kill microorganisms within the substance of the dressing can be an effective tool. They can help the clinician gain control over a difficult wound. They are not intended for long-term use. To be clear, they are not designed as drug delivery systems. They are not designed to treat infection. They are not designed as a therapeutic intervention. They are designed to stop the dressing from becoming part of the problem and becoming contaminated.

Safety and effectiveness: There are so many peer-reviewed controlled studies, some of which are registry-based studies based on thousands of patients that are published in reputable journals. For instance, a registry in the United States in an orthopedic center of repute showed a 76% reduction in surgical site infection following joint arthroplasty with these dressings as part of the management regime. Similarly, a prospective study showed a

reduction in surgical site infections from 16 to 4% in cases of excised pilonidal sinus, which by its very nature is likely to get contaminated postoperatively. And so there is good data that these devices are effective for their intended purpose.

In terms of safety, the postmarket surveillance data reveals adverse events or complaints, not even adverse events, are at 7 per million uses. And even allowing for underreporting of adverse events, we can certainly categorize these devices as safe as Class I devices.

The silver resistance issue has been covered substantially over the last 2 days, and antiseptics in general do have a lower propensity to induce bacterial resistance than antibiotics because they attack the bacterium in multiple sites. Ionic silver has a broader spectrum of antimicrobial activity than antibiotics. It is effective against most of the multi-resistant organisms. And I would remind the Panel that antibiotic resistance started only 10 or 20 years after the introduction of antibiotics, whereas silver in the environment have been with bacteria for billions of years, and they're still susceptible. There is no evidence that silver relates to antibiotic resistance.

So on this basis, we contend and suggest to you that the case for up-regulating to Class III has not been made. There is widespread evidence confirming these devices as safe and effective. There is no evidence that they pose a serious risk to health, either to society or to the individual, and therefore we suggest that Class II with special controls is the appropriate regulatory classification. And we'd be very happy to help FDA, the Panel, and other stakeholders in the development of that guidance.

Thank you.

DR. HARRIS: Thank you.

Our next speaker is Randi Rutan.

MS. RUTAN: Good morning, everyone. Dr. Harris and Panel members, thank you so

much for the opportunity to be able to speak with you today. My name is Randi Rutan, and I'm the Vice President of Medical Affairs for Derma Sciences.

Derma Sciences has 10 of the FRO products under discussion today. They were cleared through the 510(k) process without any clinical data. Due to my brief time today, I'll confine my remarks to the honey containing dressings and not the silver ones. We will be submitting written comments.

As a disclaimer, I must say that I am presenting scientific information which may be outside our label claims but is certainly cogent to today's discussion.

Honey has been a therapeutic benefit for thousands of years. Its clinical use was supplanted relatively recently due to the advent of antibiotics. Today, medical grade, UMF-rated Manuka honey is derived from the nectar of the *Leptospermum scoparium*, or the Manuka bush. It is the phytochemical properties of this plant that give the honey its unique properties. To qualify as medical grade, UMF-rated Manuka honey must conform to rigorous standards of quality and consistency. Honey impregnated dressings mechanically cover and protect the wound, help maintain a moisture balance within the wound environment, and provide the barrier to microbial contamination. Honey also provides three additional benefits to the local wound area, including acidification, free radical scavenging, and osmotic fluid movement.

The wound bed pH of a chronic ulcer is alkaline or neutral when compared to intact surrounding skin, and when the wound is kept in an acidic condition, the fibroblast proliferate more actively, and the wound's healing process is stimulated more than when in an alkaline condition. Further, lowering the wound pH by about half a unit releases 50% more oxygen locally. Topical honey helps to decrease the wound pH and helps to rebalance the wound, decreasing proteolysis and improving local oxygenation.

Activated polymorphonuclear neutrophils are attracted to the wound site and

produce superoxide anions that are then converted into hydroxyl radicals. The phenolics, flavonoids, and ascorbic acids in honey serve as protective and potent antioxidants.

Finally, due to its high osmolarity, when honey is applied to the wound, the hydroscopic quality draws fluid from the tissues underlying the wound itself, which aids in cleansing the wound bed and helping to circulate endogenous enzymes and phagocytic cells as well as maintaining a mild, moist wound environment.

Medical grade Manuka honey has been shown to inhibit the growth of a wide range of bacteria, fungi, protozoas, and viruses, including antibiotic-resistant strains. In this study of 63 DFU patients, Kamaratos reported a statistically shorter time to closure for those patients receiving Manuka honey impregnated dressings, and a significantly lower proportion developed infections requiring systemic antibiotic therapy. Further, a greater proportion of subjects had a sterile wound following the use of Manuka honey dressings than those who received standard sterile dressings -- excuse me, saline dressings.

I'm going to skip this one really quick.

Thousands of patients have received many honey dressings without any significant safety issues. There have been no reported infections or super-infections associated with their use. The combined effects of the UMF wound acidification, free radical scavenging, as well as the osmotic cleansing of the wounds combine to provide an antimicrobial activity equivalent to 13 to 18% phenol.

Blair et al. investigated the ability of ATCC strains of *Staph aureus* and *Pseudomonas aeruginosa* to become resistant to honey and controlled antibiotics. MICs and MBCs were assessed prior to and after continuous exposure to these inhibitors in this particular study. Exposure to sublethal concentrations of the antibiotics tetracycline, oxacillin, and ciprofloxacin induced a resistance phenotype in the antibiotic-susceptible strains.

In contrast, constant exposure of these organisms to an increasing sublethal

concentration of active Manuka and non-Manuka honey did not raise the level of resistance. Resistance to one antibiotic resulted in an increased cross-resistance to a second antibiotic for both the *Staph aureus* as well as *Pseudomonas aeruginosa*. As illustrated in this table here, tetracycline-exposed strains of *Staph aureus* had a 64-fold increase in resistance to tetracycline and a 32-fold increase in cross-resistance to oxacillin. When challenged with honey, however, the strains of antibiotic-resistant phenotypes remained unchanged in their susceptibility.

There is some variability in our labeling, depending upon the specific dressing type we are talking about. But in general, all of our MEDIHONEY products, the labels read pretty much as depicted here. These dressings are designed to manage a wound, helping to create an environment for the optimal functioning of the body's own reparative processes. These are not marketed for the prevention of wound infection. They are not marketed for the treatment of wound infection.

It is truly amazing to me, as a healthcare professional, that the basic principles of wound management have been known for the last 4,000 years or so. The first wound treatments were described four millennia ago, and since then, the various principles of wound care have been passed on. While we will agree with the FDA that there is a dearth of prospective randomized controlled clinical trials demonstrating clinical effectiveness and safety, this is, in general, very true of all wound care products in our practices. Honey-containing dressings have a long history of safety. They're effective within their current indications. We believe that honey-containing dressings should be considered as Class II medical devices and remain cleared through the 510(k) process.

Thank you for the opportunity to address the Panel, and I appreciate your attention.

DR. HARRIS: Thank you.

Our next speaker is Peter O'Hanley.

DR. O'HANLEY: I'd like to thank the Panel for allowing our company to make some comments, and also I'd like to particularly thank Ms. Washington, who has helped organize this important meeting.

I am a practicing internal medicine and infectious disease specialist with a Ph.D., M.D., and an M.P.H. and a former tenured professor at Stanford University. I currently serve as the Vice President of Clinical Development and Regulatory Affairs at Exoxemis. Exoxemis for the last 20 years has basically developed haloperoxidases as topical antiseptics. I'd like to make some comments about the antiseptics on open wounds.

A review of the literature and the information from sponsors, from my perspective, showed there are a number of serious problems with pre-amendment antiseptics when applied to wounds directly or via wound dressings to open wounds. There are systemic toxicity concerns due to their systemic absorption on wound beds. It should be noted, all of these pre-antiseptic -- I mean pre-amendment antiseptics are of small molecular weight. There are documented mechanisms of antiseptic resistance, except iodine. And in the case of chlorhexidine, there is definitely mechanisms for cross-antibiotic resistance. Although I would agree, in the individual patients that receive these products, that these microbes with these types of resistance patterns is not a current problem, it's true folly to think that the indiscriminate use of antiseptics for other indications besides wound care will not lead to maybe a day in which antiseptics will not be able to kill certain microbes in the wound.

My main concern is the uncertain antiseptic efficacy of the pre-amendment antiseptics, except possibly iodine for chronic venous stasis ulcers. And I believe this is probably related to the fact that the antiseptic effects are reduced in the presence of blood and exudate. From my perspective, from the published literature and lack of important information, additional safety and efficacy data from clinical trials are needed for all pre-amendment antiseptics applied directly or leached from the wound dressings to open

wounds.

I'm surprised by the FDA in that not realizing that antiseptics that leach from a wound dressing that basically go to the wound bed are not considered treatments. If the antiseptic was adhered to the dressing and not released, I can understand the concern -- I mean the claims of an antiseptic for an antimicrobial dressing preservative.

My concern is that I think it would be fair and better for patient care that approval of all antiseptics applied to open wounds, including wound dressings with antiseptics that leach into the open wound milieu, be uniform. Also, effectiveness should be based on scientific principles for wound bed preparation and should focus on the reduction of microbial bioburden and the elimination of certain microbes in the wound bed and not wound closure per se.

Because of the lack of uniform FDA guidance for antiseptics in open wounds and in wound dressings, it's probably not surprising that there have been no new classes of antiseptics developed for the last 50 years. Possibly the FDA could consider the optimal attributes of an antiseptic for open wounds one that doesn't interfere with normal wound healing, does not cause local irritation or sensitization, does not absorb after application to the wound bed, reduces wound inflammation and exudate, has broad microbicidal activity against wound pathogens, does not select for antiseptic resistance, and also has activity in wound environments with blood and exudate. Our company has actually developed such a product.

The last comment I'd like to make is that one thing that may not be realized is that the microbicidal activities of conventional antiseptics, including the pre-amendment antiseptics, at concentrations that do not overtly cause cytotoxicity or tissue damage are dramatically reduced in the presence of human blood.

This shows a time-kill study in which chlorhexidine was incubated with *Staph aureus*.

One can see that within 15 minutes without the presence of blood, that the *Staph aureus* is dramatically reduced in reduction. However, even in the presence of 2%, there's only a two-log reduction at 60 minutes and a one-log reduction at higher concentrations of blood.

Thank you very much.

DR. HARRIS: Thank you.

Our next speaker is Amy Fowler.

MS. FOWLER: Good morning. My name is Amy Fowler, and I am representing Argentum Medical here today, makers of Silverlon Dressings. We would like to thank the Panel and all of you for providing this wonderful opportunity for public comment today.

The second slide provides the appropriate disclosures.

I would like to start out with a few comments about the overall process of this Advisory Panel meeting. We greatly respect what FDA is trying to accomplish here today. We recognize the concerns that FDA has with this therapeutic category, but the effort to regulate must be balanced against the benefits, data driven, and given enough time for true medical and scientific input. Today we only had 6 weeks' notice to this hearing, and really this is a very limited format for input and discussion.

The scope and timing of the process are concerning. It is a one-size-fits-all approach. We are tasking this Panel with monumental societal, medical, and scientific decisions affecting a great number of patients, physicians, and commercial entities. We're dealing with a system that is based on problems that have not been firmly established and based upon evidence that the Agency admits is equivocal. The solutions being proposed are broad based and not tailored to individual therapy categories or even individual products within those categories.

The FDA's Executive Summary data is truly not compelling. There are a number of examples throughout the document, such as these that are provided on this slide. And

truly, there are many, many more such references throughout this entire report, attesting to the equivocal state of the data.

So let's step back and look at the big picture. Burn patients, physicians, and healthcare facilities already face numerous challenges with the resources, including wound dressings, that are available today. Classification must take into consideration that Class III designations will limit the wound dressings available in the future. We are concerned that classification of these products into a Class III designation will stifle innovation. Innovation comes from small companies, and small companies will be unable to fund clinical trials. Innovation happens incrementally, not with large leaps. Safety and efficacy of devices need to be considered for a huge range of patients, wounds, environments, and healthcare providers.

Please do not make the problem worse. This appears to be a case of "ready, fire, aim." FDA is a data-driven agency. Let's operate on data. Regulatory decisions that push devices into Class III or require additional data for marketing are the wrong decisions. Yesterday we heard several panelists agree that deciding on appropriate endpoints for clinical trials is a very difficult process. Designing meaningful clinical study protocols is difficult, if not impossible. Some products stated, or some panelists stated, that basically running a trial with a control that does not include silver or some other agent would essentially be unethical. There seems to be a presumption here that the medical community does not know what it is doing. Topical dressings actually decrease the use of antibiotics overall, fewer IV antibiotics and fewer oral antibiotics.

There are some challenges here for the proposed Panel decisions:

- The issues are too broad.
- The data at hand is inconclusive at this scale.
- The ingredients involved are too numerous.

- Safety and efficacy varies widely for each ingredient.
- The questions to be answered require a governmental study, not precipitous anecdotal action.
- The question is why the hurry?

The Agency essentially wants to lump decisions for hundreds of cleared devices, all different kinds of wounds, a myriad of microbes into a handful of big questions. What is the answer? The answer should be "It depends." It depends upon:

- Dose
- Indications for use
- Materials used and how constructed
- Clinical needs
- Patients
- Environments
- Concomitant therapies

And it depends upon more data than we have today and the time to analyze it, debate it, and draw conclusions. We ask that the Panel classify these wound dressings as Class II.

Thank you.

DR. HARRIS: Thank you.

Our next speaker is David Barillo.

DR. BARILLO: Thank you for allowing me to speak to the Panel. I'd like to ask you to move to Slide 4, in the interest of saving time, which starts with concern of the effects of regulatory changes on burn care. While we're doing that, let me tell you of my background. I have 25-plus years of experience as a burn surgeon, board certification in general surgery, plastic surgery, and surgical critical care, 12 years experience at the U.S. Army Burn Center,

including a tour as the director, and I currently do research in the use of silver products.

My first concern is the effect of regulatory changes on burn care. The United States has barely sufficient resources to manage the day-to-day care of burn patients. Burn care is extremely resource intensive, and many of our antimicrobials in daily use date back to the 1960s. The newer dressings that we use come from small businesses that cannot afford the regulatory burden of device reclassification.

Next slide. And then skip, please, to the next slide.

Microbial resistance to silver is extremely uncommon. There are four different antimicrobial mechanisms of action to silver, and you need to overcome all four to produce resistance. There were three known silver resistance genes, but the presence of these genes do not protect bacteria against high levels of silver ion.

Chopra, in a 32-year literature review, found less than 20 cases of silver resistance. Most of these were intentionally produced in the laboratory and one strain of *Pseudomonas* lives in silver mines. There have been no clinical problems in 60-plus years of burn experience with silver nitrate and silver sulfadiazine.

Next slide.

Silver dressings result in less antibiotic use, not more. By providing high and sustained levels of silver at the site of the wound or the infection, you prevent the development of microbial resistance. With silver nylon dressings, silver ion is not absorbed into systemic circulation or found in solid organs even after long-term use. Silver-based dressings at the site of the wound allow local control rather than using oral or intravenous antibiotics.

Next slide.

Microbial resistance is a valid concern. As a practicing intensivist, this is a daily problem for me. I have to always worry about sensitivity patterns. Responsible

stewardship is a good idea, but topical antibiotics are not the problem.

Next slide.

In the United States, 80% of all antibiotics sold are sold for agricultural use. And this is FDA data. Ninety percent of these antibiotics sold for agricultural use are used as growth-promoting and prophylatic agents rather than to treat infection. The FDA is appropriately worried about this.

Next slide, please.

And in 2013 came out with guidance for industry to try to limit this practice. I point out the first line says "contains nonbinding recommendation," and the second word is "guidance," not regulation.

Next slide.

So, in summary, antimicrobial resistance is a major concern for all of us. There are five millennia of human experience with silver ion, and silver ion does not cause antimicrobial resistance.

Topical wound therapies allow targeted therapy at the site of infection and decrease the use of systemic antibiotics, not increase them.

It makes no sense to further hinder the difficult work of burn care providers by unnecessarily over-regulating products that we already know are working. These products properly should be in Class II. If we reclassify wound dressings combined with drugs into a PMA category, we're going to put a lot of small businesses out of business and further restrict the limited therapeutic options available to practicing clinicians.

Rather than further regulation of the 20% of antibiotics used for human use, perhaps we should reconsider the 80% of antibiotics sold in the United States that are now used in agriculture to fatten animals rather than to treat human disease.

I thank you for the opportunity to talk to the Committee. Thank you.

DR. HARRIS: Thank you.

Our next speaker is Jeffrey Shupp.

DR. SHUPP: Thanks to the Panel for the opportunity to speak today and represent the American Burn Association. My name is Jeff Shupp. I'm the Director of the Burn Center at MedStar Washington Hospital Center, our region's burn care facility, and Chair of the Research Committee for the American Burn Association.

So a little bit about the American Burn Association. We were founded in 1967. We are currently the largest organized group of providers caring for burn patients in the world. Our membership is widely multidisciplinary, making us a unique surgical society, and we have greater than 3,500 members. We advocate for not only burn care but burn survivors, and we provide advance burn care to ensure optimal outcomes. As stated by many folks, there is a paucity of data in wound care, so we provide the best guidance that we can for burn care.

The FRO classification is a very crowded space, and it has widely different devices, which produce widespread confusion for all stakeholders. The ABA agrees with the Agency that reclassification of certain FRO devices is warranted, and the ABA agrees with the Agency that general controls alone are sometimes insufficient to assure safety and efficacy for FRO wound dressings.

Metal-based, polymer-based, quaternary ammonium compounds, and oxidizing agents do not meet the definition of drugs, in our mind. For topical silver, as stated previously, it has been medically used for millennia, has clearly demonstrated a safety profile, and there has never been evidence of a clinically significant resistance pattern in burn care.

The wound care dressings currently classified as FRO products that contain metal-based, polymer-based, quaternary ammonium compounds, and oxidizing agents should be

reclassified as Class II devices. These antimicrobials are not drugs, and special controls will be sufficient to assure safety and efficacy.

In closing, as stated previously, burn care in the United States is strained on a daily basis. If often exceeds local capacity on many days.

Burn wound care options are very limited when compared to treatment options for many other diseases.

And reclassification of the current FRO wound care dressings to Class III status would potentially have a dramatic effect on the way we care for our patients by limiting our options and possibly increasing morbidity and mortality.

Thank you very much for the opportunity to address you.

DR. HARRIS: Thank you.

I'll ask again, is Dyane Tower with us now?

(No response.)

DR. HARRIS: Okay. If not, does anyone in the audience wish to address the Panel? If so, you'd be granted 5 minutes to do so.

(No response.)

DR. HARRIS: So seeing no other members of the public wishing to address the Panel, I'd like to just give a few minutes to the Panel to maybe have additional discussion regarding these past presentations before we take our first break.

Any comments from the Panel?

Ms. Lott.

MS. LOTT: I'd just like to provide some data that supports two or three of the different speakers' comments regarding small medical device manufacturers. That is where most of our innovation in medical devices comes from, and small companies -- I saw some data recently presented by the FDA at a device conference. The FDA considers a small

company to be 70 people or less, and 90% of the medical device manufacturers fall in that, 90%, or less; 80% fall in 20 people or less. And so I just want the Panel to realize the magnitude of if we go balls to the wall and classify everything as Class III and it's going to require clinical trials, the massive impact that that will have on industry and then on clinical practice and the availability of these products.

DR. HARRIS: Dr. Alam.

DR. ALAM: I think the presentations were interesting. I have a couple of, I don't know, questions/comments. One was with regard to classifying these into Class II or Class III. Given that FDA feels strongly Class I is inappropriate, it would be interesting to hear from FDA now or later, to what extent it's feasible to split the category we're looking at into further subcategories, whether there are particular features that may be associated with higher risk that might potentially lead something to being more Category III, given that the preponderance of these devices don't seem to pose substantial risk. And even though it would be nice to get more data on them by forcing them to be Class III, I don't think that's a reason to do so. But I'd be interested in seeing if there's any way to split them up that seems rational.

The other question/comment pertains to the claims that the manufacturers currently made. I think there's been a lot of confusion and struggle at the Panel level and maybe in other venues as well, trying to understand the difference between what's happening in the dressing and what's happening in the patient. And it seems like some of the current claims are almost designed to I wouldn't say obfuscate the issue but kind of gloss the issue, and if we could sort of separate that and make the claims very clearly pertaining to the dressing, I think, in my view, that would be important for me to feel comfortable assigning a Class II or suggesting that a Class II rating be assigned to these, because sometimes the claims almost seem like we're only treating the dressing, but the

claim can easily mislead some casual reader into thinking that there's some treatment going on.

DR. ASHAR: This is Binita Ashar.

I think you had asked about how we could potentially subcategorize some of these things to regulate them rationally. FDA has proposed considering physical form. As you know, the solid, the ointments, and the wound washes is possible categorization. We would encourage the Panel to consider other categorization, either considering a device description based on the chemicals that are included in the dressing and also possibly physical form, also considering the indications. So if you find that there is a subcategory in this lot of 700 that makes sense for which you can put a box around, then that's what we would like for you to do and to delineate to us how you're looking at benefit/risk within that box and the things that would fall outside of that box.

DR. HARRIS: Dr. Patel.

DR. PATEL: Thanks. I wanted to make a comment based upon some of the presentations and the description of antimicrobial resistance. So I think it's important to remember, so specifically for silver, there are plasmid-mediated mechanisms of resistance for silver. These are efflux pumps. That means that the bacteria is able to actively pump the silver out of the cells so that it doesn't have antimicrobial activity. I think there were discussions about how it's possible to apply higher concentrations of silver to overcome that resistance, and that may certainly be the case. I do think in the age of antimicrobial resistance that we're living in, we have to worry not just about resistance to the active agent but also what other types of resistance are being co-selected. So on a plasmid, there are multiple resistance mechanisms. It's rare to find a plasmid these days so it just has one mechanism of resistance. So if you're selecting for one, you're bringing along another, and that other one might be very devastating in some cases.

DR. HARRIS: Dr. Reller.

DR. RELLER: In follow-up to the presentations, the comments that we've just heard, and in anticipation of the questions coming, I'd like to know from FDA how many, if any, of these hundreds of products are under discussion here as a PRO [sic] because they're in a combination with a device. How many of those combinations have the second component, not the primary mode of action, the dressing, the gel, etc., but as the secondary component a compound that if it were alone would be under the purview of CDER? In other words, in some of our consideration, an antibiotic or an antimicrobial. We're not talking about a disinfectant that has antimicrobial activity, but a drug that is cleared for human therapeutic use in a different context that is a component of a PRO combination device. Are there any, and if so, how many, and what are the drugs? And we don't need a complete answer now, but I think that it would be very important for the discussion and the questions coming up subsequently.

DR. ASHAR: Okay, you've asked a lot of questions, and so I'm going to try to do my best with it, and others can help me.

So in the FRO category, many of those are the devices plus a chemical. There are also things that were not discussed here, devices plus a chemical for hemostatic use, and those are off the table. I think there are other entities in the FRO category, but the vast majority are with chemicals that we're talking about here. Some of those chemicals are monograph drugs, the agents in monograph drugs, but not a whole lot of them. And a lot of the chemicals that are present could be, if you were considering the chemical itself for the proposed -- I don't know how that would work. But if you took out the chemical alone and wanted to claim some therapeutic benefit to us, those would be considered drugs, albeit probably new molecular entities. And perhaps my drug colleagues can also chime in.

DR. SHERMAN: I can try, and maybe the Office of Chief Counsel will help. So, first of

all, for the monograph, some of them are not being used, or many, according to the monograph. We can get you numbers after the break. So therefore, they would be unapproved new drugs because they're not being used in accordance with the monograph. For the ones that are not monographed and if they are not approved by the FDA for that use, then they are again unapproved drugs. They may be new molecular entities, in other words, never approved for anything or not approved for that use.

The other point that I didn't make very well or I somewhat misspoke before, if it's going to be a drug claim -- this is what Dr. Ashar was getting at -- it's a combination of the product itself and the claim, no matter which paradigm we're in. So a drug claim, for example, prevention or reduction of risk of infection or treatment of infection, that's a drug claim. So even if the dressing were the primary mode of action, you still have to meet the drug standard for that drug claim. Does that help you?

DR. RELLER: What I'm trying to get at -- this is to be a simple example. Are there any of these combination products that contain, for example, a tetracycline, aminoglycoside, I mean something that we would consider -- well, are considered therapeutic agents specifically? And if there are no -- that puts quite a different light on the classification of Class II or Class III, regardless of whatever the other implications are of recommending a reclassification.

DR. SHERMAN: So it sounds like you'd like us to give you a short list, if we can, of the -- so silver -- tetracycline or maybe bacitracin or maybe polymyxin, those compounds, we can do that.

DR. RELLER: Yes. And there may be others. I mean, some of them may have been used historically that are no longer used because of adverse effects that have been in the literature related to that. I mean, I think there were compounds historically -- this is going back decades -- where gentamicin was used for topical burn therapy, and the

aminoglycoside resistant, high-level resistant to gentamicin, this complicated treatment of enterococcal endocarditis, for example, are some of the fallout effects of those practices that I don't think anybody does anymore.

Has anybody used kanamycin, I mean, a cephalosporin in kanamycin for irrigation of wounds or high-volume neomycin washes? I mean, these are things that I don't think are done anymore, but they have been done in the past, and there has been well-documented toxicity or unintended societal resistance consequences that have occurred. And that's what I was getting at, the specificity of the issue without getting into exactly what the concentration of silver is or this or that, but rather something that might change a view on classification.

DR. CHANG: This is Cynthia Chang.

I'd like to provide a little more clarification on the types of ingredients that have been considered drugs in wound dressings combined with drugs in this FRO category. If you refer to Appendix 2 of your Executive Summary, if you still have that, there is a list of most of the ingredients that have been considered as drugs and cleared in these products. Ones that may be considered active ingredients in approved or monograph drugs include:

- Allantoin
- Bacitracin
- Behenyl alcohol
- Benzocaine
- Cadexomer iodine
- Calamine
- Chlorhexidine
- Dimethicone
- Hydrocortisone

- Hydrogen peroxide
- Iodine
- Iodoform
- Lidocaine
- Manganese chloride
- Polymyxin B sulfate
- Potassium iodide
- Povidone-iodine
- Salicylic acid
- Silver sulfadiazine
- Sodium fluoride
- Tromethamine USP
- White petroleum

So as you can see, there is a variety of active ingredients that have been considered approved active ingredients and approved drugs or monograph drugs in some form or function. However, the inclusion of those ingredients in these wound dressings have been cleared through the 510(k) process throughout the years.

DR. HARRIS: So we'll start with Dr. Miller.

DR. MILLER: I want to springboard off of Dr. Reller's question and ask about how the FDA handles these things. If we decide, or if you decide, that FRO devices should be Class II, what happens if somebody comes up with a device which contains vancomycin or some clearly, you know, inappropriate antibiotic for wide distribution because of resistance? I mean, can you say that's got to be a Class III? Do you have that prerogative?

DR. ASHAR: This is Binita Ashar.

So in the 510(k) flowchart, we first look at intended use, indications for use. We also

look at a technological comparison between the subject device -- in this case, for example, it would include vancomycin -- as compared to the predicate device. Given that there may not be a predicate device that has vancomycin in it, that would start a menu of questions associated with what we know about vancomycin, if it may be kicked out of the 510(k) flowchart for that reason, because then we start asking questions about whether the primary mode of action is the device or if it happens to be the drug. So it actually not only kicks it out of the 510(k) flowchart, raising questions about whether it should be regulated as a 510(k), but it potentially could also trigger questions regarding jurisdiction, as to whether it should be regulated within the Center for Devices or if it should go to the Center for Drugs.

DR. HARRIS: So Dr. Burke.

DR. BURKE: I just wanted to ask, of the submissions for the 510(k), about one-third were rejected. So why were they rejected? Were they rejected because of what we've just been discussing; they might have medicines? Do they have new compounds that haven't been investigated? Or do they just not meet the criteria that they say they meet by the testing they present? So can you categorize why things have been rejected in the past?

DR. ASHAR: This is Binita Ashar.

If I'm understanding the question correctly, Dr. Burke, you might be referring to one of the presentations where we talked about the clearances to date and why some of them were not cleared. There was a graph that represented that.

DR. BURKE: Yeah, there was a graph showing that approximately one-third are not cleared. So our question is, certainly, if it has a real antibacterial rather than antiseptic, the ones we were just discussing, would that not be cleared? If it has a new compound that -- do some of them have new compounds that haven't been really studied or something that just doesn't meet the criteria of testing, of the bacterial testing that we discussed in detail

yesterday? So I kind of wanted to know why have things in the past been rejected.

DR. ASHAR: This is Binita Ashar. I'm going to try to answer part of it, and then I'll turn it to Dr. Chang.

I think you're asking two questions here. One is for what reason would a wound dressing not be cleared, be found not substantially equivalent? And the other question has to do with maybe background information regarding the graphical representation that we provided in yesterday's presentation.

So with respect to why a product would be found not substantially equivalent, it could be for any number of reasons. It could be based on a different intended use or indications for use. It could be that the technological comparison demonstrated that it was not substantially equivalent, perhaps with respect to lacking performance testing. And in that performance testing, as we covered yesterday, it could include an assessment of biocompatibility, sterility testing, as well as some of the other more clinical claims that you're talking about here, albeit that they're limited to the dressing itself.

And so I'm wondering, Dr. Chang, could you talk a little bit about how that graph was developed?

DR. CHANG: So I believe you're talking about a graph of the number of submissions received as well as cleared each year from 2000 to 2015, from yesterday; is that correct? So I believe there are a number of reasons that a submission would be received but not cleared, some of which were just discussed by Dr. Ashar. Other reasons may be that there just was not enough information in that submission, and there is a delay as we request more information. In terms of having submissions received in what year, they may be cleared the next year, for example.

DR. BURKE: I just want to clarify my question. I understand the criteria, but of the one-third rejected, what percent -- do you have any idea what percent was just they didn't

meet the criteria? Or were there some with a new compound that didn't meet the criteria, but it's a new compound, so that's a different kind of question? And the third thing, did any of them have gentamicin and therefore they were maybe bumped up to a different class or not cleared because it's too strong? It's not an antiseptic now, it's a real antibiotic. So I just wanted to know, because going forward, it was part of this question that we don't want to go forward and say that we like things in Class II if certain things will be included that we might not mean to be included at this Panel.

DR. CHANG: So I do not have the numbers of what was bumped out of the classification or group of products for various reasons. I want to say that, going forward, you have a list of many ingredients that have been cleared, and you have the opportunity to comment on what you think are appropriate within ingredients that have been cleared, as well as to comment on technological characteristics and risks and intended uses that you believe would be appropriate in a certain class or would be appropriate in a different class. And so if there are specific concerns, risks, or ingredients that are of particular interest to you, you will be asked to discuss that in the questions this afternoon.

DR. HARRIS: Dr. Sood.

DR. SOOD: Thank you for this interesting discussion. I just wanted to add a little bit of the clinical aspects of resistance because this is something, as a hospital epidemiologist, we deal with all the time, and I would suggest and propose that perhaps we want to stratify the risk of resistance because we talk about resistance very broadly, and it's a very scary term, but it means a lot of different things. There are a lot of hospital surfaces, devices and equipment, that have been proposed to be coated with copper, and there's copper resistance that has been noted in bacteria, and transfer of plasmids in the environment in hospital rooms as well. So I think there is a lot of different mechanisms of resistance and a lot of different components that cause resistance.

An example of something that we do: This is a risk assessment that we do in our own institution and hospital epidemiologists also think about. An example is coated catheters for central lines. There's a difference between how we use coated catheters with chlorhexidine, which is more of an antiseptic and not something we're going to be using for treatment of a patient, versus use of minocycline-coated antibiotics, minocycline-coated catheters, because minocycline is an antibiotic that we could use therapeutically. So among my hospital epidemiology crowd, most of us favor using coated devices with agents that aren't used for therapeutic mechanisms later on in the future.

So my suggestion would be that perhaps we want to subclassify the Class II into those that actually have antibiotics, as Dr. Miller pointed out, and then separate out those that have antiseptics, that the resistance may be in a stratified approach, still there but maybe not as a big of a concern.

DR. HARRIS: Okay. Well, if there are no more comments, we're a little ahead of time, which I guess is okay. It's 10:05. We will take a 15-minute break and ask everyone to be back at 10:20.

(Off the record at 10:05 a.m.)

(On the record at 10:20 a.m.)

DR. HARRIS: If everyone could please take their seats, we're going to resume our meeting. So we're going to begin with a few comments from Dr. Ashar.

DR. ASHAR: Thank you, Dr. Harris.

I just wanted to clarify a comment that I made earlier in my enthusiasm of describing the 510(k) flowchart and how we assess these products, as we look at a product in the 510(k) framework. To clarify, I think what I did is I lumped intended use and indications for use together for the Panel that is largely clinically oriented. However, I need to step through a little bit more carefully on that point.

When we look at a new product, and if it's being reviewed under 510(k), first we will compare the intended use to the intended use of the subject new device. And if that intended use is substantially equivalent, then we will move on to compare the indications for use to the proposed indications for use of the subject device.

Now, when we look at the comparison of intended use, if the intended use is different, it would kick it out of the 510(k) paradigm. If the intended use is the same, we would go on to compare indications for use. Now, that indications for use may be not exactly worded like the same indications for use of the predicate device, but it could be substantially equivalent. And so then we could make a determination that we could move forward with subsequent review of the technology comparison between the predicate and the subject device. This is just an important distinction from a regulatory perspective because the determination that the intended use is the same is of significance because it indicates to us whether or not we can review this device under 510(k) or not. Hopefully that clarifies things and doesn't confuse it.

DR. SHERMAN: And if I could also try to make a point of clarification. We're having a very lively internal discussion at FDA. So these being combination products, that's what we're discussing, and the dressing is a device component; the other component is a drug, and taking silver as an example, it is not an approved drug. So this is a little bit of our conundrum; it's not been studied as a drug. So I think that's why we're all struggling with this notion it's doing something to the dressing. But one of our speakers in the Open Public Hearing did bring up the question of absorption, systemic absorption. Certainly, I think, with lidocaine and -- we'd all want to think about that pretty carefully. And we think you're gradually moving toward bucketing probably different risk levels, and we're very interested in hearing that. But again, just to reinforce the point that it's a combination with a drug, and these are not approved drugs.

DR. HARRIS: Dr. Sayeed.

DR. SAYEED: So I have a question for the FDA, just to follow up on these points. What percent of the intended use products go on to the indication for use, and what percent of the indication for use go on to become Class II drugs? And the reason I ask that is because, you know, if we base our opinion on these drugs on Class II devices today, then do we open up this bucket of other devices trying to be approved as Class II without systematic reviews of evidence on safety and efficacy?

DR. ASHAR: Okay, I don't think I have percentages to share with you. I think in looking at bucketing these today, I think you should consider the intended use, and in describing that intended use, you know, giving us examples of the claims that would go along with your concept of that intended use would be very helpful. And, you know, the next thing we do in a 510(k) review would be thinking about the device description and the technological comparison. So within that bucket, after you've considered intended use and some of the claims, what types of technology should be within that bucket and why you think that the benefit/risk profile would be reasonable, and what you think FDA should do to assess and characterize that benefit/risk profile with some of the risk mitigation measures that you may be proposing.

While I haven't answered your question directly, hopefully, by giving you this framework, it gives you a sense of what we're looking to accomplish.

DR. HARRIS: Dr. Reller.

DR. RELLER: In the discussion briefly today, and certainly yesterday, one of the putative benefits of these dressings was reduction in antimicrobial use. Do any of these PROs have a claim for that in the indications or the package insert or what -- so it was discussed as that's a benefit, but currently there are no products have that claim in their labeling?

The reason I ask that is because it is conceivable to me that when it comes to the classification discussion, that there might be an additional option, and maybe it falls into the controls, but that is that if these conditions exist, that the claim should not be allowed, and it would be a mandatory relabeling of the intended use based on the substantive evidence that it does what it claims to be doing so that we're not forced into it because there may be those who are skittish about putting too many things into Class III. But if there were an option to get a more accurate description of what they do and they don't do in the indications that doesn't -- you know, there's limited control on how they ultimately are used if they're cleared, but nonetheless theoretically one should be able to be held -- and certainly the guidelines try to do this, that a product is used in conformity with what it's indicated for.

DR. HARRIS: Dr. Alam.

DR. ALAM: I had one question for FDA and then also a brief comment. The question was -- and maybe I missed it, and I apologize if I did. Can you clarify or give some examples of the difference between intended use and indication, because I'm not exactly clear on how that would work.

And then the comment was, in terms of trying to put this in different buckets, one way to maybe do this would be to hold out -- and I think maybe Dr. Reller was getting at this -- the prospect of more substantial claims being linked to going through the premarket approval pathway. And that could potentially not be so much of a stick for manufacturers but an incentive, because then they would be able to say, well, our product has been shown to do this, which the bulk of products which are Class II cannot say.

DR. ASHAR: I wanted to try to address both Dr. Reller and Dr. Alam's questions. With Dr. Reller, I think it is very important to not only characterize what would be within each of these buckets, but what would, in your mind, fall outside of the bucket. That's just

as helpful, if not more.

The other thing is with respect to claims regarding reduction in antimicrobial drug use, while we don't have those claims in these devices currently, if you feel that this is an important claim and you think that there is a mechanism by which these studies may be conducted, if you have suggestions, please provide those.

While it may not necessarily affect how any sort of regulation is crafted, the meeting minutes are going to be used by several individuals both within and outside of the Agency. So your thoughts on this matter would be helpful in guiding study development.

Dr. Alam asked about an example, perhaps, of an intended use and indications for use, and so this is quite hypothetical but pertinent to today's discussion on these products. So perhaps considering for some of these dressings that it is intended as a barrier, that could be an intended use. And indications for use may be some of the things that Dr. Marquart put up on the screen yesterday. So it is intended to serve as a barrier indicated for X number of days to provide moisture to the -- you know, some more detailed description of what the indications for use are. If a product doesn't have the same intended use as the predicate device and we cannot review it, looking at that cited predicate as being a valid predicate, and if there is no valid predicate, we can't review it under 510(k).

DR. HARRIS: Okay, I think we'll move on now to another presentation from FDA. I'd like to invite Dr. Chang back to the podium.

DR. CHANG: Good morning again. My name is Cynthia Chang, and I am a biomedical engineer serving as the senior lead reviewer in the Plastic and Reconstructive Surgery Devices Branch 2. In my presentation today, I'll be providing a discussion of the three subcategories of wound dressings combined with drugs. This is to provide background for the classification questions you'll be answering for the remainder of the day.

As an overview of my talk, I'll begin with the scope of products for the classification

discussion, what products are included and excluded. Then I will review the composition and indications that characterize the three different subcategories of wound dressings combined with drugs, as well as the risks FDA has identified for each group and potential mitigation measures. The risks posed by each product type and the potential mitigation measures for each risk are critical components for determining the appropriate classification, whether Class I, II, or III, for each type.

So moving on to the scope of products for the classification deliberations today, please remember the focus is on wound dressings combined with drugs. These are unclassified pre-amendments combination products in the form of a solid; gel, cream, or ointment; or liquid wound wash. There are a variety of ingredients present in cleared products in this category, including active ingredients in approved or monograph drugs, chemicals that may be identified as inactive ingredients in approved drug products, other chemicals with antimicrobial activity, plant drug materials and botanical extracts, and other additive components including salts, surfactants, and thickening agents. Please note that the conditions of use and indications for use vary from the drug approvals and monographs. A more comprehensive list of ingredients is present in Appendix 2 of the Panel Executive Summary.

What is excluded from the scope of the classification deliberations are other products which are not wound dressings combined with drugs in the product code FRO. This includes the interactive wound dressings, which are Class III and regulated under product code MGR. These are wound dressings that are life supporting or life sustaining, intended to replace the full function of skin, and are intended to accelerate or promote wound healing through active interaction with the wound. Further, unclassified wound dressings that are composed of animal-derived materials and which have new drugs, dressings combined with biologics such as thrombin and hemostatic wound dressings are

excluded from the scope of this classification discussion.

Now that we have defined the general scope of the classification discussion, I'll move into the three subcategories of wound dressings with drugs and their risks and mitigations. Some of this will be a review of information presented yesterday.

The first is the solid wound dressings. Solid wound dressings are composed of various synthetic or naturally derived materials and can be biodegradable or non-biodegradable. They can be in the form of a woven or non-woven fabric pad, foam, or hydrogel that has sufficient structural integrity to hold a physical form, such as a scaffold and matrix. Some dressings are multi-layered, with each layer made of a different solid material. Typically, these dressings contain added antimicrobials.

Solid wound dressings are generally intended for covering a wound, protecting against external contamination, absorbing exudate, and providing or supporting a moist wound environment. These dressings are typically cleared for use on a variety of wounds. These wounds may or may not be colonized with microbes or be infected. Some dressings are indicated for use to cover and protect catheter insertion sites or other percutaneous device insertion sites. Some are cleared for management but not treatment of infected wounds.

The potential risks to health that FDA has identified for solid wound dressings are presented here. As discussed in Laura Marquart and Karen Nast's clinical presentations yesterday, there is a potential for adverse tissue reaction, including toxicity, allergic reaction, irritation, and sensitization, as well as delays in wound healing due to the composition or formulation of the product. The dressing may have incompatibilities with other therapies, depending on the characteristics of the materials or the drugs present.

When there are added antimicrobials, there may be an increased risk of it contributing to antimicrobial resistance, as discussed in detail by Brandon Kitchel and

Professor Gottrup in their scientific and clinical presentations yesterday.

Use of the dressing may lead to infection, whether due to the dressing composition and material properties or how the dressing is used, for example, if it's not changed frequently enough. There are other risks related to the material properties of the dressing which could be compromised.

Many of the solid wound dressings serve a barrier function, whether providing a physical barrier to external contaminants, fluids, or debris, or as a microbial barrier as demonstrated through bench testing. If the barrier function is lost prior to or during use, adverse consequences may result for the patient.

Similarly, many of the solid wound dressings which contain antimicrobials have a claim that there is an inhibition of microbial growth within the dressing. If the antimicrobials present are ineffective for the claimed antimicrobial or preservative function, this may result in microbial growth within the product.

Additionally, the product may degrade during storage, whether due to degradation of the base material or the added drug or both, which may result in a product that is out of specification being used on a patient or delaying therapy while a replacement is found.

Finally, dressing material may be retained in the wound during use if the entire dressing is not removed, or if all of the dressing pieces are not removed, if multiple pieces are used.

For these identified risks, FDA has identified the following potential mitigation measures. These mitigation measures could potentially be established as special controls. Special controls can be established only if the risks and product are sufficiently understood to ensure that the risks can be adequately mitigated and assure safety and effectiveness in light of available scientific evidence.

The risk of adverse tissue reaction could be mitigated by an evaluation of

biocompatibility. As mentioned in my presentation yesterday on the current regulatory pathways for wound dressings, biocompatibility evaluations for these products typically involve an assessment of the toxicological risk of the ingredients as well as cytotoxicity, irritation, and sensitization. Depending on the ingredients or drugs in the product, additional toxicity assessments such as chronic, systemic, and genotoxicity and pyrogenicity testing may be conducted.

For the risk that the dressing may delay wound healing, an in vivo animal wound healing study could be provided to demonstrate whether the product has this effect.

The risk of incompatibilities with other therapies could be addressed through labeling, which provides adequate contraindications, warnings, and precautions regarding potential interactions with a product or its components.

Regarding the increased risk of contributing to antimicrobial resistance, there is a potential to address this risk by evaluating and identifying the risks and potential mechanisms for resistance development. This could be performed through a literature review specific to the antimicrobial in question and its proposed use in the product. Additionally, contraindications, warnings, and precautions in the labeling could assist clinicians in deciding when and how to use the products appropriately.

The risk of infection would need to be addressed through a variety of methods, including labeling instructions regarding appropriate patient monitoring and care, as well as testing to validate the shelf life of the product. For a sterile device, testing could validate the sterilization method used. For a non-sterile product, preservative effectiveness testing could demonstrate that a low bioburden is maintained in the product.

To address the loss of barrier function, in vitro bench testing could evaluate whether the dressing is effective as a microbial barrier or whether the dressing effectively prevents water loss or acts as a barrier to external moisture, depending on the particular claims.

The risk of microbial growth within the product could potentially be addressed through antimicrobial effectiveness testing, as discussed in detail by Brandon Kitchel on Day 1 of this meeting.

For the risk of product degradation during shelf storage, this could be mitigated by labeling which identifies the shelf life and which warns the user not to use a product that is not intact or is discolored. Shelf-life validation through testing could also be provided.

And for the risk of retention of the dressing in the wound, it may be mitigated by labeling which reminds the clinician to check that the entire dressing has been removed during dressing changes, or to count the number of pieces of dressings used.

Gels, creams, and ointments are the next category of wound dressings with drugs. They are amorphous and can have high water content with thickening agents or consist of an oil-water emulsion. Many of these wound gels, creams, and ointments contain plant-derived materials or botanical extracts. These products typically contain added antimicrobials. They are generally packaged in tubes or containers that can be for single use only or labeled for multiple use after the package has been opened. They may or may not be sterilized.

Gels, creams, and ointments are generally intended for use to provide or support a moist wound environment. These dressings are typically cleared for use on a variety of wounds. Some products are cleared to relieve the symptoms of skin irritation, such as dryness, itching, and pain, by providing a moist wound environment. The types of skin irritations include various types of dermatoses.

The potential risks to health that have been identified for wound dressings in the form of gels, creams, and ointments are presented here. These include the same risks discussed for the solid wound dressings:

- Adverse tissue reaction;

- Delays in wound healing;
- Incompatibilities with other therapies;
- Increased risk of contributing to antimicrobial resistance;
- Infection;
- Microbial growth within the product; and
- Product degradation during shelf storage

You'll notice that omitted from this list are the risks of loss of barrier function and retention of dressing material in the wound. This is because the gels, creams, or ointments do not have the same ability to maintain a barrier in the way that a solid dressing does, and as gels or emulsions, there's not the same risk of leaving behind a solid piece of foreign material in the wound.

The mitigation measures for the risks are the same as those discussed for corresponding risks for the solid wound dressings.

The third subcategory of wound dressings with drugs is the liquid wound wash group. Wound wash solutions are liquid in form and are typically water or saline based. These wound wash solutions may contain various salts or surfactants as well as added antimicrobials. They are generally packaged in bottles with plain caps or pump sprays, and they may or may not be sterilized. Products have been cleared with antimicrobials as preservatives to minimize microbial growth during shelf storage or multiple uses after the package has been opened. Products that do not contain antimicrobials are sometimes sterilized and labeled for single use. Some products may contain antimicrobials but also be terminally sterilized.

Wound wash solutions are intended to rinse or irrigate a wound to physically remove foreign materials such as debris and wound exudate. Additionally, they have been cleared for physically irrigating away microbes, debris, and exudate from the wound. These

products are typically indicated for use on a variety of wounds.

The risks FDA has identified for liquid wound wash solutions are presented on this slide. They include the same risks presented for the gels' risks and ointments, including:

- Adverse tissue reaction;
- Delays in wound healing;
- Incompatibilities with other therapies;
- Increased risk of contributing to antimicrobial resistance;
- Infection;
- Microbial growth within the product; and
- Product degradation during shelf storage.

There is an additional risk as well, due to the intended use of this subcategory to physically rinse or irrigate a wound. There is a risk of the product's inability to remove wound debris or foreign materials.

As for the mitigations for the identified risks, they are the same as those identified for the other two dressing categories with corresponding risks. For the risk of the product's inability to remove wound debris and foreign materials, it could be addressed through labeling which instructs the user on how to appropriately use the product to achieve the intended effect. Additionally, bench performance testing could be conducted to demonstrate that the product, when used properly, such as with a spray bottle, has the appropriate physical characteristics to remove debris.

This concludes my presentation on the three subcategories of wound dressings with drugs which you will be discussing today. You will note that while there are a number of similarities for these three groups, there are enough differences due to their physical form, intended use, and risks that FDA has asked you to comment on each group separately.

Thank you.

DR. HARRIS: Thank you, Dr. Chang. I'd like to thank the FDA in general for these presentations.

Does anyone from the Panel have any clarifying questions for FDA?

Ms. Lott.

MS. LOTT: Thank you. Michelle Lott.

So before we get started in breaking down each subcategory and the classifications, I had a question for the FDA about two guidance documents, that one is still in draft and one is final publication status, and about their relevancy on the process that we're about to discuss.

So the first is draft guidance for industry and FDA staff, premarket notification 510(k) submissions for medical devices that include antimicrobial agents. This guidance was issued as draft on July 19th, 2007, and it specifically has got the FDA's current state of thinking at the time about how to control any product that has an antimicrobial added to it, specifically -- and it's very consistent with what the FDA, specifically Brandon, presented yesterday, being characterization of the antimicrobial agent, identity and formulization, concentration, method of application to the device, mechanism of action, antimicrobial activity spectrum profile, release kinetics of antimicrobial agent, minimum effective concentration, toxicity. It also has requirements for biocompatibility and allowances for bench testing, animal testing, and even clinical testing.

And then the guidance document for one of the other wound dressings containing the pDADMAC adds to those with biochemical testing, for barrier testing and quantitative testing, along with outlining risks to health.

So where do those fall in our discussion today as possibly not reinventing the wheel but deciding what needs to be added to those to provide an adequate level of special controls? So maybe this is a good starting point for our conversations, or does FDA not

think that these are relevant anymore?

DR. ASHAR: This is Binita Ashar, FDA.

With respect to the draft guidance document, as with all our draft guidance documents, those are available for public comment. And while it reflects some of our thinking on the topic, it's not one that we're asking manufacturers to necessarily comply with. So I think it would serve the Panel as food for thought.

With respect to pDADMAC, it's the one device in -- it's one of the wound dressings -- it's the only wound dressing in the Class II category, and it went through the de novo process, and so the risks and mitigations are outlined there, as you've referenced. Again, that would be great food for thought to the extent that it can inform your discussions today.

DR. HARRIS: Dr. Sayeed.

DR. SAYEED: So in terms of the three categories here, labeling is prevalent throughout all three of them. We all know that labeling has its issues in terms of, you know, doctors using the labels, patients understanding the labels, good communication through the brochures. If labeling on these products is problematic, what else can the FDA do if this is a Class II product? What other assurances can the FDA give the Panel on protecting the public?

DR. ASHAR: I may have one of the lawyers comment. So I actually wanted to go back to something Ms. Lott mentioned first, that is, with respect to pDADMAC that went through the de novo process. It, like these unclassified products, didn't have a classification. And so we determined it was appropriate to be in the Class II category, and it went through the de novo process, creating a regulation for it, which developed the benefit/risk list that you're seeing and referencing in that guidance document, just to give others on the Panel the definition of or a sense of what de novo means.

With respect to labeling, we expect our manufacturers to be truthful and accurate in the labeling and to comply with the way that we've regulated these products. And so it would be very helpful to us for the Panel to comment on what you see as being appropriate labeling for a given category of products that you think have a comparable benefit/risk profile, and what types of claims you think falls out of that categorization so that we can hold manufacturers accountable and manufacturers are also aware that this was the spirit with which any new regulations have been crafted.

DR. SHERMAN: But just to add to that, Dr. Chang has done a very careful job of delineating for you the tools available to us, and a part of your discussion is going to be what you think of those tools and what you think they can provide us. And just to remind everyone, we don't have rescission authority, so our decisions stand, so we're going to listen very carefully.

MS. LOTT: This is Michelle Lott.

To speak to Dr. Sayeed's question, when labeling is introduced as a special control, it's an entire section of a guidance document. And so they would take what we tell them is important in the labels and incorporate that into a guidance document. So it's not just a free-for-all where industry gets to necessarily choose what they put on their label. They do, but they have minimum requirements. For instance, in this guidance document I was mentioning on the antimicrobials, there's a whole page and a half or so of the content that has to be in the labeling. I don't know if that speaks a little bit to -- and it goes into a great bit of detail about the type of bacteria that have be identified, the genus, target pathogens, the chemistry of the product, so on and so forth.

DR. HARRIS: Dr. Alam.

DR. ALAM: Murad Alam.

I appreciated the talk, Dr. Chang, going over the mitigations that could be used for

these various different types of products within this large category we're looking at, FRO category.

I guess one comment I would have, and maybe it's also a question, is when -- this is how it's a question -- is when does the number and extent of mitigations become so extensive that we are approaching Category III level of regulation? Because one of my concerns would be that while we definitely do want to have, at least in my opinion, adequate regulation for products, for products where we have only a theoretical risk of potential outcomes that are adverse, which I think is many of these products -- we're worried, but we don't have a lot of solid data -- I'd be reluctant to add so many hoops for manufacturers to jump through that we were sort of de facto making it a Category III.

DR. CHANG: So I think that's an excellent observation, and thank you for the question. In answering, I guess, the questions regarding risks and potential mitigation measures this afternoon, I want you to remember the information that is currently reviewed for these products, which include the intended use, the technology, certain performance testing such as biocompatibility, antimicrobial effectiveness testing, toxicity, and in some cases animal and clinical testing. And so in addition, labeling is also a part of the review. However, we do not have special controls established for what is required. So there is something that is done currently. In the future, for special controls, we could lay out exactly what we would like for manufacturers to meet. Important to that discussion is that we sufficiently understand the risks, the technology, and how mitigation measures could be adequate to address the risks and deciding if something would be appropriate for special controls. So that's really part of the main calculus that you have to do.

DR. HARRIS: Ms. Leach.

MS. LEACH: Fluryanne Leach.

I just wanted to comment on Dr. Sayeed's concern about the labeling, and I think we

need to be aware that no matter how good the labeling is from the product standpoint, how well do practitioners pay attention to that labeling? And I think that's pretty problematic in my experience. So that should play a part in our thinking.

DR. HARRIS: Dr. Campbell.

DR. CAMPBELL: Yes. So it was a very nice talk about mitigation of risk. Could you clarify for me also the possibility -- although not necessarily in this discussion, but is it not true that for special controls, one of the special controls could be a request for clinical data? And I think in the presentation yesterday by the FDA, this point did come up. You might have even said that it was fairly rare for these wound dressing products. I wonder if you could say a little more about the few cases where there was clinical data associated with the clearance of these 510(k) wound dressing products, FRO.

DR. CHANG: Thank you for the question on the requirement for clinical data in a 510(k) or the potential to require that as a special control. Yes, we may choose to include a requirement for a special control to require a clinical study if, you know, based on the Panel discussion today and additional information, we feel that that's necessary. We have requested and based clearances of 510(k) wound dressing with drug products on clinical study data. The 510(k) summary is our public summaries of the basis of our decisions, and any cases where these decisions are based on clinical data, there is a description of the study, number of patients, and outcomes that led to our decision. One example that was highlighted yesterday by Dr. Marquart was that for a specific claim of reduction of, I think, CRBSI, which is catheter-related bloodstream infections due to the use of a wound dressing as a barrier for a catheter insertion site, there was a clinical study conducted on 584 patients in a controlled study. Does that answer your question sufficiently?

DR. HARRIS: Dr. Holmes, you had a question?

DR. HOLMES: It really wasn't a question; it was more of a comment. In response to

Ms. Leach, the answer to that question is 80% of what practicing physicians do on any given day is off label. So this is where regulatory science and medical science diverge. What it says on the label, what it says on the indications, that's to ensure that there is global safety and we don't end up with another thalidomide. What happens once it's on the market, that's what the free market decides. And you know, from a small business perspective, there's a $70 million average difference between the cost of a 510(k) and a PMA.

DR. HARRIS: Dr. Reller.

DR. RELLER: Barth Reller.

Only tangentially related perhaps, but if I recall correctly, yesterday there was an allusion to antimicrobial agents being removed, restricted, recommended from soaps, and I asked because of two things. One is it would -- presumably underlying that was the societal effects on microbiome in doing that. Microbiome has been, I think, mentioned once in these discussions, but this is another aspect that has caught, to some degree, the popular imagination. Blaser et al. There's a lot out there, and what we are doing to our microbiome by actions, and that is relevant to this day's discussion and decisions. So exactly what was done, and what were the implications, the consequences, the action; how was it done, and on what basis was whatever action was done, done?

DR. SHERMAN: Yeah, you're referring to Dr. Califf's comments about two points, one that we have to consider that although perhaps some of these agents in these wound dressings might have a very, very low propensity, if you will, to potentiate resistance, we're talking about a huge population can be exposed, and that was the first point.

The second point, he talked about the Executive Order and what the various components of the HHS agencies are doing, and he mentioned restricting antibiotics in cattle, and he talks about coughing calves all the time now. And in particular, he mentioned the rule. CDER -- and my colleagues from OCC will correct me if I say it incorrectly -- passed

a rule that bans 19 ingredients that were in over-the-counter soaps, and they did that on the basis of lack of any data supporting efficacy.

DR. RELLER: And could you mention some of those 19 compounds, because they may be more dramatic than some of the -- I mean, we're talking about a secondary component to a primary mode of action in a dressing, a solid and its variants, you know, the lotions in it, the variants, emoluments, etc., and the washes. And so I think it is a very important concept.

DR. IKONOMI: Hi, this is Pranvera Ikonomi from CDER.

There were two reasons that those 19 active ingredients were banned. One was that we didn't have sufficient data in demonstration of safety, and the other, there was no evidence that these ingredients were more effective than just plain soap and water. In terms of what those ingredients were, some of them are triclosan, triclocarban, povidone-iodine. There are 19, so those are the three that come to mind for the time being.

DR. RELLER: Let's see. Right in front of me here is the appendix, and I circled some of these things. So not necessarily all 19, but I'll just read down a list of some of the things that have been alluded to. In the 19, was bacitracin one of them?

DR. IKONOMI: Not that I recall, no.

DR. RELLER: Polymyxin?

DR. IKONOMI: No.

DR. RELLER: Silver compounds?

DR. IKONOMI: No.

DR. RELLER: Sulfadiazine? Now benzalkonium?

DR. IKONOMI: Benzalkonium chloride, benzethonium chloride, and chloroxylenol were three ingredients that were deferred from the final ruling for the reason that sponsors have agreed to submit all the data required for safety and effectiveness.

DR. RELLER: From clinical trials or from other bases?

DR. IKONOMI: They have promised to conduct clinical trials in terms of effectiveness, and that's why the result is pending on those three.

DR. RELLER: Some of the other disinfectants on here -- I've already mentioned silver. Crystal violet, gentian violet, copper compounds.

DR. IKONOMI: No.

DR. RELLER: None of those?

DR. IKONOMI: I know what's not on the list.

DR. RELLER: Okay.

DR. ASHAR: If I can interrupt, that's irrelevant.

DR. RELLER: Okay, benzalkonium chloride?

DR. IKONOMI: I'm sorry?

DR. RELLER: Benzalkonium chloride?

DR. IKONOMI: As I mentioned --

DR. RELLER: Yeah.

DR. IKONOMI: -- benzalkonium chloride was one of the three --

DR. RELLER: Was among those.

DR. IKONOMI: -- that was deferred.

DR. RELLER: Right. So soaps, hand washes used by millions, it was prescribed to take them out or show efficacy?

DR. IKONOMI: Well, on the proposed rule, we asked for efficacy as well as safety data, and we gave the sponsors almost a year and a half to submit data.

DR. RELLER: Right.

DR. IKONOMI: And on those 19, there were no data that were submitted. Now, on the three that have been deferred, there have been some data submitted during the

process of being reviewed and others in which the sponsors have agreed to complete, in terms of demonstrating the safety and effectiveness of those three ingredients.

DR. RELLER: Thank you. I thought I recalled correctly, and you've affirmed and delineated very clearly what the current status is. Thank you.

DR. IKONOMI: Okay, thank you.

DR. HARRIS: Dr. Sood.

DR. SOOD: I just wanted to make two comments. First of all, I understand the comparison between what's being used in over-the-counter hand hygiene products. I presume that these products would be used under medical care by physician supervision. Is that a fair assumption?

DR. CHANG: Some of these wound dressings with drugs are indicated for over-the-counter use for minor wounds that would not require a physician's attention, and the majority are indicated for prescription use. I do want to point out that while there are similarities in some of the antimicrobial agents that were just discussed and some of the ones that are in the wound dressings with drugs here, FDA really considers products in the context of their intended use and the patient conditions that they're intended for.

DR. SOOD: Okay.

DR. CHANG: And so that's part of what we're thinking.

DR. SOOD: Thank you. And the second comment was just to follow up on the clinical -- how much we follow indications for use. And I would like to echo Dr. Holmes's point, but to sort of explain that that's often because it's not always possible to get the indications that you're looking to use. Especially in infectious diseases, there are very few studies on *Pseudomonas* and *Acinetobacter* LVAD infections that have been done to be able to say this is a specified indication for use. So you have to extrapolate on the data that are there. So just to add that it isn't out of poor clinical judgment that things are used off label,

but mostly just because we need to expand the role that we have indications for.

DR. ELMORE: Susan Elmore here.

So just one comment about the hand washes. The National Toxicology Program looked at some of those chemicals, and they were endocrine disrupters. So for some of them, I know that it was a large class, but just as a comment.

And so my question for you is, is it true that if a device has an active interaction with the wound, then that would require it to be labeled as Class III? Is that true, from what I've heard today?

DR. CHANG: If the intended use of the device is to actively accelerate or promote wound healing, then that would be a Class III intended use.

DR. ELMORE: Intended use. But if unintentionally -- I guess my question is for some of these devices that we're looking at, there could be an intentional interaction with the wound, because I guess I'm not clear how, without testing, we could be sure there would be no transfer of the material from the dressing to the wound.

DR. SHERMAN: Rachel Sherman.

That is one of the points we would like you to -- you know, when you get into your deliberations, because the question of systemic absorption of antimicrobials, of topical anesthetics or topical -- so it is something we'd like to hear your thoughts on.

I need to clarify a point that was made earlier. Let's say, in theory, that was the only special control you were worried about, that's the kind of clinical -- a PK study might be the kind of clinical data one might see as a special control as opposed to studies of healing, which would bump you into a Class III.

DR. HARRIS: So are we still asking clarifying questions? Okay, Ms. Lott.

MS. LOTT: So I had a question about the 19 that were the antimicrobials and then the three that are still remaining for later judgment, pending the sponsor safety and

efficacy data. Is each company who is wanting to continue to legally market those products having to submit independent safety and efficacy data? Is there some sort of industry study or institute study that's getting together or -- I'm just trying to understand the possible ramifications of any decisions we may make here, where -- is it then going to be a comment upon maybe 500 separate manufacturers to do individual testing on their products that might be all the same or on the same thing? Does that make sense?

DR. SHERMAN: This is Rachel.

Can I give you an example under a different device field, the drug-eluting stent study that was required by FDA? It was a consortium of, I believe, five device companies and three drug companies. So the FDA very much encourages collaborative research to answer questions.

MS. LOTT: But then only the manufacturers that participate in that research have access to that data and can use it in their submissions?

DR. SHERMAN: That's more of a question for OCC, of what is generalizable knowledge and what can be -- have referenced, but we can hear the specifics.

DR. IKONOMI: I think if I understood your question correctly, you were asking if the sponsors will have to provide the data individually or collectively?

MS. LOTT: Yes. Like somebody getting together to provide one set of data that all industry can use for those three chemicals.

DR. IKONOMI: Yes. And the answer is yes, they have the option of providing -- and they're actually providing those data collectively.

MS. LOTT: So it's just like -- but really, it's out of the goodness of their heart that they're sharing this data because, on the device side, everybody could stay in their little silo and then have to do individual testing.

DR. IKONOMI: But if it's a monograph active ingredient, then those data would be

public at one point, or the data would be used to --

MS. LOTT: Yeah, I'm just projecting the potential fallout for the medical device industry compared to how this situation --

DR. IKONOMI: Okay.

DR. ASHAR: This is Binita Ashar.

If I could add a comment here. I think your point is well taken. We want to make sure that, you know, whatever you're proposing, you understand what the ramifications of that proposal is, what they are. And so perhaps when you get into the deliberations regarding how you want to bucket various groupings of them -- and the groupings actually, you know, you could say some of them need to be Class II, some of them need to be Class III because these intended uses appear to us to warrant a higher level of scrutiny. That's just an example. And then you could ask us at that time, you know, what are the ramifications of some of these risk mitigation measures that we're putting in place? And I think then it will be more targeted in more directly answering the question so that you can provide the recommendations.

DR. SHERMAN: Just to repeat something Dr. Califf said yesterday, just as we are obligated and do a risk and benefit, we don't consider cost. Again, the Committee will advise us based on the risk and the benefits to the patient and to society.

DR. ASHAR: Yeah, that's a great point. I mean, the risk mitigations are what the risk mitigations are. And so if the Panel comes forward with a list of risk mitigations, I mean, that's what we're going to be paying attention to in the Panel transcript because we wanted to make the correct scientific decision.

Going back to some of the questions that Dr. Reller asked, the team is preparing a list of some of the OTC -- or the OTC -- the antiseptic washes and some of the OTC monograph or the drug list, that you have those to refer back to.

DR. HARRIS: Dr. Sayeed.

DR. SAYEED: So in terms of Class II devices and some of the control measures, Dr. Campbell brought up a great point about having clinical data as part of the Class II categorization. Are there any other examples empirically that the FDA has used other than clinical data? I mean, that sounds like a great idea. And could we ask for a time frame on receiving clinical data, just like with the soaps? What was it, 18 months or 24 months?

DR. CHANG: I think there are multiple parts to that question. So the first is are there examples of other types of clinical data that we have reviewed; is that correct?

DR. SAYEED: Other types of control measures that you could use, other than -- Dr. Campbell had brought up clinical data. You know, obviously, you have labeling and you have all of these other mitigating controls. What are some other examples that aren't on these lists that the FDA has used empirically that the Panel could consider? Because I think that, you know, I for one don't know other measures. I mean, are there other things that the FDA has used?

DR. ASHAR: I think we talked about this in general terms as best, I think, that we can. I think when you get into specific intended uses, specific claims that would fall into a particular bucket, looking at the benefits and the risks and the risk mitigations, then I think the Panel can walk through and say, well, actually, for this intended use, say it's to reduce odor and it's a barrier type of dressing, we think that patient-reported outcomes is going to be important. So I think walking it through clinically -- you know, this Panel was assembled for your expertise, particularly in the clinical arena. And so that is really where we're seeking your advice.

You know, the timeline will follow our precedent. We will deliberate over that. But I don't think that those things are unique to this circumstance. That's a process issue that we deal with on a regular basis. So really what we're looking for is your expertise related to the

risks and how we should mitigate those risks, giving us ideas about what you might want to see in your case, as a clinician, considering caring for a patient and selecting one of these products for these intended uses.

DR. HARRIS: Dr. Reller.

DR. RELLER: Barth Reller.

I'm fully aware that soap and the devices under discussion are not the same thing. However, given that the two arms of the FDA, CDER and CDRH, to the extent possible that it shouldn't be perceived that there are different standards of scientific rigor between the components of the FDA, therefore, if there is a scientific basis for requiring the efficacy of the addition or the lack of efficacy of an addition to a soap for its intended use, it seems reasonable to me, at least, of those things that are potentially proscribed or put on the watch list, that there should not be an inconsistency between those additive ingredients and that they're actually doing something in a dressing lotion or wash. If X ingredient is not shown to add anything to saline or to the solid -- whatever the example is -- then it seems to me that there's not a basis for adding it to soap, but we don't have to follow that standard for adding it to a dressing. That seems sort of incongruous to me. Not that that dictates what our decisions will be, but at least that should be a consideration in the classification.

DR. HARRIS: But a critical difference there is -- I think the statement being that there was no added benefit to adding those agents to a soap in terms of the soap's intended use to wash your hands, as opposed to maybe adding them to a protective dressing or the other indications. So I don't know that that's an apples-to-apples comparison.

DR. RELLER: Well, I'm not so sure because the question is not that there isn't utility, usefulness, value to the dressing and the lotion, etc. To me the question is does adding this compound or that improve on its intrinsic value in the care of patients with wounds? And

to that degree, it seems to me there is an analogy between the two. I mean, I presume there's a scientific basis for the action on the part of CDER. What I'm asking is do these compounds that we're discussing add something to the base product itself, for the intended use of that base product?

DR. HARRIS: So I want to just finish up our clarifying questions to the FDA, and then we can get into our deliberations. Any other clarifying questions for the FDA right now?

Dr. Miller.

DR. MILLER: Thank you. Mike Miller.

I just would like to understand better how to weigh in things like decades of use for these things. Those aren't systematic studies looking at the safety and efficacy, but they have been used for decades and some things for centuries. So we're now approaching this with a new kind of rigorous fashion, but how do we appropriately factor in that experience?

DR. HARRIS: Once again, I don't think that's a clarifying question for the FDA. I think that's why they brought us together, to hear our opinions on exactly those topics. So I think that's an important question.

DR. MILLER: Okay.

DR. HARRIS: But I don't want to have that discussion right this second.

Any other clarifying questions regarding the presentations from FDA this morning? Otherwise we're just going to move now to open the floor to our panel of experts to deliberate on any of these issues we've been talking about, including the question you just asked, Dr. Miller.

Although this portion is open to the public observers, public attendees may not participate except at the specific request of the Panel Chair. Additionally, we request that all persons who are asked to speak identify themselves at that time.

So it may seem like a technicality, but we are now opening to our deliberations. So

Dr. Miller, may you please rephrase your question or your comment?

DR. MILLER: Okay. Do I need to restate my question about that?

DR. SHERMAN: I'm sorry. Rachel Sherman. I can try and answer that. And again, I would look to my colleagues.

So it's easier to answer that -- well, it's easier at least for me to answer that in the setting of drugs. So in 1962, Congress decided that anecdote, which was not enough, and passed the efficacy amendments and the DESI process to look at what was on the market, was initiated, and somewhere between 1,500 and 2,000 compounds that had been in use for years and years and years, many of them were removed for lack of efficacy. So that, I think, is the only -- we can look at more recent examples where belief was then -- and common practice -- well, now transplantation for women -- breast cancer comes to mind, where when it was finally studied, it was deemed to be harmful. So I think we are often -- in the case, the Medical Device Amendments permitted grandfathering, and CDRH is assiduously going through, for every one, the key process of trying to classify these into classified products. So the length of time on the market perhaps is not that instructive. I don't know if anyone wants to answer that.

DR. HARRIS: Dr. Hickerson.

DR. HICKERSON: I appreciate your comment, but yet in your own literature, when you're going through seeing what fits into Class II and Class III, you list as valid scientific evidence significant human experience. And if we're going to back to 350 B.C., I'd have to say that probably stands for significant clinical human experience.

DR. SHERMAN: Well, again, as Dr. Ashar pointed out -- and I think Dr. Harris said, that's why we're having this panel, to hear your opinions, and certainly, we heard a lot yesterday about standard of care and how these products are used. But I was trying to address specifically Dr. Miller's question with the data that we have on that.

DR. HARRIS: Right. And I'll also just point out that there is a distinct difference between human exposure and clinical experience. People can be exposed to things for thousands of years. It doesn't necessarily mean that we characterized the specific impact of that exposure.

DR. ASHAR: Dr. Harris, I had a comment. I think what Dr. Hickerson was mentioning is what came from this morning's training session, and I just wanted to read the definition of valid scientific evidence with respect to device regulation, 21 C.F.R. 860.7(c)(2). Valid scientific evidence is defined to include "well-controlled investigations, partially controlled studies, studies without matched controls, well-documented case histories, and reports of significant human experience with a marketed device from which it can be fairly and responsibly concluded by qualified experts that there is reasonable assurance of safety and effectiveness of a device under its conditions of use."

DR. HARRIS: Dr. Alam.

DR. ALAM: One thought I had along those same lines is that even though the statement that was just read suggests that the evidence should be very specific in addressing the particular claimed indications, I would urge FDA, if they are going to potentially reclassify some of these combination devices and if they're going to look at mitigations, to consider clinical evidence in the form of cohort studies, clinical trials, possibly even controlled trials that may already exist for some of these products. And while they might not be precisely the trials or studies that FDA might have wanted if they were being done de novo, I still think in some cases there might be a substantial body of knowledge, the preponderance of which is sufficient to allay some of the concerns regarding specific mitigations. And I would urge FDA not to discount that because otherwise we run the risk of medical waste in research and doing lots of stuff over again for just a minute difference.

DR. HARRIS: Dr. Sood.

DR. SOOD: Just a question. The FDA, do they get safety data from silver dressings? Like are those reported? I believe I remember seeing in the presentation yesterday that that is the case, that there are safety -- like if there are adverse effects, they are reported to the FDA.

DR. CHANG: Yes, as part of required medical device reporting, manufacturers and, I believe, other required reporters must report adverse events for these products, including silver dressings.

DR. HARRIS: I'd like to ask a question to Dr. Elmore, but to the Panel at large as well. Under the special -- what do you call them? The special --

UNIDENTIFIED SPEAKER: Controls.

DR. HARRIS: Controls, thank you. The question came up that a mitigation for the risk regarding delay in wound healing could be an in vivo animal study, and I was just curious of other Panel members' opinions, including Dr. Elmore's, whether you think that's actually true. In other words, can I derive a reasonable degree of comfort that looking at the impact of some combination dressing on delayed wound healing in a rat or a pig would be equivalent to what I would see in a diabetic or a chronic smoker?

DR. ELMORE: So to answer your question, the simple answer is yes. I think that there have been studies, and we do have diabetic rat models, and I think that the responses in terms of healing, tissue healing, has been comparable to what we see in humans. Of course, the pig is the better model, but the rat is an easier model to work with, and there's already a model available for that. So yes, that would definitely be an option.

DR. HARRIS: And so the differences in terms of the structure of the skin of a pig versus a rat is seemingly not a concern because when you make a wound in a rat, it's a full thickness wound.

DR. ELMORE: Right.

DR. HARRIS: Whereas we're not usually looking at putting these dressings on full thickness wounds in diabetics. Well, I guess there could be some, but --

DR. ELMORE: That's true. But in the rat diabetic model, there are ulcers that are induced that are very similar to what we see in humans, and it's very comparable.

DR. HARRIS: Thank you.

Ms. Lott.

MS. LOTT: Dr. Elmore, you just mentioned that the model is available. Like how so? How does one go about seeing that or getting access to that to be able to further use it in support?

DR. ELMORE: It's in the literature. I can share that document with the Panel.

MS. LOTT: Yeah, possibly for the comment section.

DR. ELMORE: Yeah.

DR. HARRIS: Dr. Sayeed.

DR. SAYEED: From the consumer perspective, I have reservations of just only using an animal model for human final product end use. You know, obviously, those models wouldn't be generalizable to the human condition. They're not large studies. We can't find out differences in ethnicities and gender and all of the things that we need to be looking at. From a public health perspective, we should be looking at large robust studies that get at specific issues like healthcare disparities, like all of the things that I just talked about.

Thanks.

DR. HARRIS: Dr. Patel.

DR. PATEL: So there are other claims that also concern me if they were based upon just in vitro data or an animal model, and specifically that would be barrier against microbial entry into a wound. I wonder if that could adequately be assessed without clinical

trials basically.

DR. HARRIS: Dr. Elmore.

DR. ELMORE: So to answer your question, yes, you could use an SPF rat model, and you know, there are already models available, wound models available in rats, but the dressing would be applied, and then the bacteria would be applied on top of that, and that could be tested. So, you know, you would use, like I said, an SPF model. So, you know, of course, the pathogens are different in humans and in animals in their environments and on their skin. But if you wanted to test a specific pathogen, that would be easily done.

DR. PATEL: If I could just respond. So what I worry about is that the entry of the microbial pathogens isn't just from the top down, you know, from the outside through the dressing to the wound, that it's often happening through the individual's skin and the microbiome that exists on the skin, which would be different from a human to an animal.

DR. HARRIS: Dr. Holmes.

DR. HOLMES: Well, actually, the mechanism would be identical, and none of the dressings that are in the FRO category claim to stop it from coming through the sides, because if they are claiming that, they're claiming to be active in the wound bed itself, and that would make them Class III.

DR. HARRIS: Dr. Alam.

DR. ALAM: It's Murad Alam.

I think one thing that several people have touched on before is the issue of the specific claims that are being made, and I think we're alluding to that again right now, and I think it's been raised before, that patients and even physicians may not really be reading the indications for these products carefully enough to know the difference between what they're supposed to be doing, which is protecting the dressing, and what some people might think that they're doing, which is repairing the skin. So I think one option -- and I'm

not sure this is a good idea; I'm just floating it as a potential option to clarify that -- would be potentially to include claims or comments that were stated in the negative, saying something, that this product has not been -- I don't know exactly how to parse it. I'm sure that would require some thought. This product has not been sufficiently studied to show that it improves rate of wound healing or directly impacts the skin wound or something like that. So I think that would be a bit of a red flag to somebody who was using the product, to understand that while it might be safe and effective, its indications were somewhat narrower than they might anticipate.

DR. HARRIS: Dr. Reller.

DR. RELLER: To follow up on Dr. Holmes's comments, it is my understanding that the direct entry through a dressing, of the patient being at risk from what's coming through the dressing is relatively unimportant pathophysiologically as opposed to the skin flora, whatever it is, the usual expected skin flora or the veneer of -- it's been stated that the whole world is covered with a veneer of feces; it's just thicker in some places than others. And I think that's where surgical wounds, I mean that whole concept of -- I mean, these are understood by everybody around this table. That's where the problem is.

Now, you can say, well, the product does not claim to prevent the ingress of the altered microbiome. However, when I state that my product, if I were to state my product is a barrier to infection that's effective, I think the implication is that it's a barrier to infection, and I'd like to know myself, if that statement is made, that in fact that the second ingredient has some effect on that process, apart from the base dressing, etc., a wash, this concept of added benefit, for whatever the claimed benefit is, of the added ingredient as opposed to the intrinsic value of the wash, etc.

DR. HARRIS: So I'd like to suggest for the Panel that we maybe spend a few minutes describing or discussing what might be some basic principles that we could try and apply as

we move forward this afternoon in our discussions regarding classification of these different products. And it seems like, as I've been listening to the discussion, that one of the issues of importance seems to be whether or not these dressings contain agents that could be potentially absorbed into the wound. It seems to be there's also a question of whether the agents that are being combined with these dressings, or the products, have been previously studied and cleared as independent agents or not; whether the indications for the product are therapeutic or non-therapeutic; and then concerns regarding what occurs in the real world in terms of are people really reading the indications for use of these dressings. I don't know how many people actually read a bandage before they apply it.

So with that in mind, and perhaps I've been incomplete in my summary, but I'd like to maybe have us talk along the lines of how we might think about those issues and whether that will help us as we approach the heavy lifting of classifying these products.

Ms. De Luca.

MS. DE LUCA: Somewhat anecdotal, truly anecdotal, there's another doctor often in the patient's room, and that's Dr. Granny. And when I had my first surgery in 1972, I had bandages from the sides up, down, and she came in, she was born in the 1890s, and she came in with this little bottle of salve. You couldn't stop her if you were an elephant, and she was a little tiny thing. And I think sometimes we don't realize that she went home and boiled the lamb and got the fat and did whatever it was she did and brought it back, because I couldn't stand the itching. I was just in tears from the itching of the bandages and everything. I think sometimes Dr. Granny is in the room more than we know, whether she's physically there or remembering there or something that mentioned growing up that the family just does. So it's not always the physician, but somebody else adding to it.

For the Panel to think of the instructions that you're reading on labels, the reading level is too high for most people that go home with the label on their product, and they

don't have -- five syllables, that's never going to be read. You know, three syllables, we're probably talking about the third grade level, and it's just something that also has to be put in here. The patients must recognize that the label is there. It's not written by God, but close to it. It's written by their doctor or written with their doctor's advice, but they just can't -- because they can't read it, it doesn't mean they should make it up.

DR. HARRIS: Ms. Leach.

MS. LEACH: I think Ms. De Luca has brought up a good point. There's a whole group of people between the doctors and the patients who use these products, and when a doctor -- and I understand that doctors often use products for things that they're not specifically indicated for. But when they order that product to be used, they're not the one putting it on the patient necessarily, and all of those layers that go down through nurses, nurse's aides, therapists, maybe home care or maybe the patient, if the patient is doing their own wound dressings, may not be reading the indications or the directions for use. And so they are or can be used incorrectly, not intentionally but -- or people just do things unthinkingly that would nullify the effect that the dressing or the cream or whatever is supposed to have.

And I think that we all need to remember the statistics for good hand washing and how that affects the use of some of these items as well. If you go and put one of these dressings on when you have not washed your hands -- and I have seen situations where people, both doctors and nurses and therapists, go from one patient to the next, examining their wounds, putting new dressings on, without washing their hands. How is that affecting this product? Is this product going to prevent any microorganisms that may be on those dirty hands from getting into the wound? Yeah, we have a concern that it's not going to come from the sides, but is it really going to do what it says it's going to do by protecting from other sources of contamination?

DR. HARRIS: Dr. Miller.

DR. MILLER: Thank you. Mike Miller.

I think in an issue like this that's really very complicated and we have everyone from grandma to the nurses and everyone else who has a role in this, that we have to try and limit our considerations to exactly what is on the table here and what the FDA's role is. And the FDA's role is not to police all of medical practice and make sure practitioners are following the label and make sure -- the FDA has a very specific and limited role here, and that's just to look -- in this specific question, we have a dressing which is not supposed to be interacting with the wound, so all of that is off the table. All the discussion about lowering infection rates and even reducing antibiotic usage, I don't see that as a relevant thing here. That's an interactive dressing, and we're not supposed to be talking about that. So I think that we need to be looking exactly at those four criteria at the beginning of the session. You know, does the addition of the agent prevent bacteria overgrowth in the dressing and things like that? I mean, that's very addressable, and we can look at that specifically. How the practitioners use it, whether it's of value in the patient care, there are other ways that sort it out.

In my institution, if I use a dressing that costs three times more than just a simple piece of gauze because it has an agent in it, I'm going to have to justify it to a whole list of people at my institution of why I'm using that. They're going to make me do a comparative study. They're going to make me do a variety of things to show that the extra cost of the agent is making a difference in the patient care. Now, that's a local thing, that's right in my hospital. It doesn't necessarily have to involve the FDA. It doesn't have to involve society as a whole. So all of these things are combining together to make sure the patient gets the right care, and our question here before the Panel is what specific role does the FDA have to play on this specific thing?

DR. HARRIS: So I'd actually like to allow FDA to respond to that because I share your general opinion, I believe, that the FDA is not in the business of practicing medicine. But I am also interested to know how the FDA thinks along the lines of once you become aware of how people are using products in clinical practice, does that have any influence from a regulatory perspective?

DR. SHERMAN: Hi. Rachel Sherman.

I'll start, so first, to the role of FDA. FDA does not police medical practice; we don't regulate medical practice. Absolutely correct. But I think, to Dr. Reller's point, we feel very strongly if we're adding something, it should be for a reason, and we should understand what that is, and we should communicate it. So I don't personally know, but the drug statutes -- but it again has to do with what the purported effect is and how it's communicated.

Now, to your second point, if we become aware that one of our risk mitigation strategies -- and first and foremost is labeling or something else -- is not effective and there's harm or risk of harm, then we need to take action. I'll give one drug example, and then I'll turn to my device colleagues for device examples. So there was an NSAID in '98 that was -- if it was used less than 10 days, it was fine. If it was more than 10 days, you know, you'd rot the patient's liver. So a box warning, the prescribing practice didn't change, and we pulled it off the market or it was voluntarily withdrawn, yeah, at our request.

So yes, we don't -- if there's a satisfactory alternative and something is causing harm, that's one. If there's no satisfactory alternative, we may again accept more risk. In this case, we are very much talking about -- and this is the hard part. We're saying, okay, we're going to isolate this dressing, and we're going to add something, and then we're going to ask all of you to tell us whether that makes sense. So we understand why you're struggling.

DR. ASHAR: This is Binita Ashar.

I don't have too much to add. I think under optimal conditions, we would like to ensure that the testing that's performed on these devices in the premarket informs the marketing and the marketing materials, and that those marketing materials inform clinical use, and all of those three things are aligned. And when we have cases of mal-alignment, questions come up as to what's the benefit, what's the risk, what's the risk of that mal-alignment for us to consider what additional actions we need to take.

I wanted to mention one thing because communication was discussed on the patient level. And so in some instances, FDA, of course, with our over-the-counter products, we have patient-specific labeling. But for other prescription sorts of devices, we also have patient labeling, and so in some cases, that could be a potential recommendation of this Panel.

DR. SHERMAN: If I could just add two points. Whatever is said, it has to be truthful and not misleading, or it's misbranded and we can take action and see -- the other point is just, in your discussions yesterday and today, it's been very clear that the majority of you, if not all of you, believe there is a pretty robust dataset on some types of dressings for catheters, and how does that impact your thinking? If there's a class of products that now has been well studied and there's, you believe, an established benefit, how should we be thinking about that versus some of the others? That would be very helpful to us.

DR. HARRIS: Dr. Sayeed.

DR. SAYEED: I just want to add to what Ms. Leach and Ms. De Luca said. In terms of off-label use in these wound care products, we have to remember that people that are using these wound care devices aren't in academic centers. These are occupational clinics across thousands of worksites across the country. These are community hospitals; these are community clinics. Oftentimes they'll see thermal burns, they'll see chemical burns, and you just grab the first dressing you can grab and put it on the patient. And whether or not

it's appropriate or not, that is up to the purview of the FDA. They can tell us, with a high level of studies, that yes, we can use it in this indication, we can use it in this particular use, but we can't do that without evidence.

DR. HARRIS: Dr. Hickerson.

DR. HICKERSON: Thank you, sir.

In response to the aspect of these dressings being utilized in those type of clinics, the majority of the times these are too expensive, and what you're usually seeing put on the wounds, burns, and other traumatic injuries that are seen there are going to be Silvadene, bacitracin, and things like that that are not what we're really talking about. In my institution, I would venture to say that there are less than 0.5% of those outlying clinics are hospitals, large hospitals that would have that type of dressing, this type of dressing that we're talking about, to put on burns and wounds like that.

To go back, Ms. Sherman, I think that this would be a great indication for the registries that we've been talking about, to go back and collect some of this additional data that you're looking to have that would answer some of your questions from the standpoint of safety to the public, because then you'd have the data across the board, not in just select populations, but those that you could pull out and get the information that you're needing for your safety data with that as well.

DR. HARRIS: Dr. Alam, then Dr. Reller, then Dr. Hunt.

DR. ALAM: I'd like to address the question that Dr. Harris had posed, which was how to deliberate based on some of the questions we've already come up with, some of which we've been discussing right now, as to the potential issues with regard to reclassification. And my suggestion would be that if we solely focus on deliberating on all of the ways where these devices, these combination products, sorry, are potentially problematic, our discussion will be biased. It will be biased because we'll just discuss the potential problems,

and pretty much it will seem like there are only potential problems. So I think even if we can't give it equal time, we have to at least consider the countervailing arguments why, in fact, the current classification scheme may be okay.

DR. HARRIS: Dr. Reller.

DR. RELLER: Dr. Harris, if I could, I'd like to ask a question of Dr. Gottrup.

Dr. Gottrup -- and I can pass this down, and it doesn't have to be answered immediately, perhaps for early this afternoon's discussion. But I would be curious to know -- and the basis is the belief that scientific evidence is universal -- if any of the products on the FDA appendix list are prescribed by European regulatory agencies in the care of wounds.

DR. GOTTRUP: I must say that I'm not aware of that, and I can't make it directly. I have to go into it and find out which ones because it's a long list you're showing me there.

DR. RELLER: If you had a chance, perhaps you could read it. The reason that I ask this of you is if I recall correctly from your presentation yesterday, that you said we don't do this in Denmark and --

DR. GOTTRUP: Related to what?

DR. RELLER: No, in the wound. I don't remember the specific -- I'd have to go back and review the slides.

DR. GOTTRUP: Okay.

DR. RELLER: But it had to do with we do not incorporate antibiotics into this dressing.

DR. GOTTRUP: It's antibiotic itself. Antibiotic itself directly in the wound, in a dressing or directly, whatever you do, isn't forbidden. That's a rule that all microbiologists has been set in order to get rid of the resistance we have. And it's antibiotic, antimicrobial besides that, antiseptic, whatever it is.

DR. RELLER: So are there any -- there are at least -- well, there are two, anyway, on this list that are antibiotics: bacitracin and polymyxin.

DR. GOTTRUP: Bacitracin we don't use.

DR. RELLER: They're not used, or are they proscribed from a regulatory standpoint?

DR. GOTTRUP: We cannot use it. We will not put it into the wound because we look at this as an antibiotic.

DR. RELLER: No, I understand. But that's the clinical belief, you know, or is there an edict from some regulatory agency, either national or Pan-European, that proscribes the use, for example, of polymyxin directly or in the vehicle of a dressing?

DR. GOTTRUP: What we are discussing now and saying, it's in Denmark. It's all microbiologists who has been interested in wounds. You actually showed the picture of the professor, which is one of the leading microbiologists in Denmark, who actually had decided -- and whatever you can say, I think he has put up in his mind and looked at the evidence and from that set -- our rules in local Denmark, not only in Denmark, is that we'll not use antibiotic topically in wounds.

DR. RELLER: So it would be another way of saying this is the standard of practice in Denmark?

DR. GOTTRUP: Absolutely.

DR. RELLER: And the importance of this, in part, is because Denmark, the Netherlands, Scandinavia, as you alluded to yesterday, have been in the vanguard, way before things happened here, in the proscription of antimicrobials in animal feeds, etc. And clearly the astounding -- I mean, I realize it's complicated why you would have such low rates, but it's astounding the differences in Europe between the countries with low resistance rates and what is different about them, and I think it's relevant to what we're doing here.

DR. HARRIS: Dr. Hunt.

DR. HUNT: So a couple things. One is that you can also buy antibiotics over the counter in Europe that you can't buy in the U.S., so I'm not sure that we can isolate the discussion just to the wound products.

In terms of the categorization of the products, it does seem to me that the dressings intended for central venous catheters should be considered separately. There is a lot of randomized controlled trial data in that regard, and I think that other wounds are so much different from central venous catheters that that should be considered differently.

And then to follow up on what Dr. Hickerson was saying, I think the registries will be of critical importance because to do randomized controlled trials for all of these types of products is really impossible because there are too many factors that you can't control for, and you can't stratify for enough things like obesity and diabetes. You would have to have sample sizes in randomized controlled trials that are prohibitive for any type of meaningful study. But registries could be very important. And again, you have the overlapping considerations of the use of systemic antibiotics at the same time that these wound care products are being used that cannot easily be controlled for in clinical randomized controlled trials. So registries are really what will be of critical importance to understand the clinical benefit.

DR. HARRIS: But to Dr. Miller's earlier point, a clinical registry would be looking for therapeutic value as opposed to the non-therapeutic function or operation of the dressing itself, which is presumably what we're here to discuss.

DR. HUNT: Well, I thought, like we talked about a little while ago, that we're not talking about therapeutic benefit for these, that that's not what the wound care dressing is intended --

DR. HARRIS: I'm just trying to clarify. What would be the information we would

obtain from the registry?

DR. HUNT: From registries, you could obtain information about risk to the patient population and benefits and other measures of clinical benefit for the patient. If you're really trying to find out if the dressing actually has any therapeutic benefit, then I think yeah, you would have to do a randomized controlled trial. But that would be so challenging to do unless you had only one type of wound and it had only a certain size and the patient was at a certain weight and had no diabetes or no other underlying factors. If it's in the lower extremity, they couldn't have any significant vascular disease because that would impair wound healing in terms of, you know, vascular supply to the wound. I mean, there are just so many factors there.

DR. HARRIS: Right, but all of those factors, as the Commissioner pointed out yesterday, is what randomization is designed to address and that same -- all of those factors would be present in any registry that you dealt with as well. So I think that registry information could be very, very valuable provided it was adequately granular to provide the information that you needed to collect prospectively. Otherwise, it could just be a morass.

DR. HUNT: And registries -- yeah. And generally that's what registries do; they give you the information that you can then take to study in a randomized controlled trial. But I don't think that there's any way -- you can't control for everything in randomization, and we know that at the end of a clinical trial, that often we get new information that we can't apply to that trial because we didn't include that as part of a stratification, and we find that the samples are actually imbalanced for certain factors that we didn't consider and stratify for or control for. So there are a lot of those factors within this population. That's why I'm saying trying to lump and group so many things together makes it really difficult.

DR. HARRIS: So we had Dr. Hickerson, then we'll go around the room.

DR. HICKERSON: To answer Dr. Reller's question, though, I think what he was asking

earlier was are any of these dressings also in the EU? And the answer to that is yes. Just a quick search brings up at least three that I found with silver products that's sitting over there in the EU.

DR. HARRIS: So Dr. Campbell.

DR. CAMPBELL: Greg Campbell.

So I like the idea of registries, and I think registries are great and that they can provide a lot of information. And this sort of goes to the big data idea, the idea that if we collect a lot of data, we'll be able to answer a lot of questions. The caveat I would offer, though, is good registries don't just happen by accident, and what you really want in a high-quality registry costs a lot of money. And so if you look at the registries that are successful, and there are very few, they are usually the effort of industry, of medical societies, and they just don't happen by accident. CMS has played a role in the creation of some of the registries. But the notion that, for example, the medical device wound care industry will pay for these registries without some encouragement in terms of postmarket requirements from FDA is very unlikely.

So I really like the idea of a registry. I think the choice is not, though, between registries and randomized trials. There are lots of other kinds of uses of data that can be used. And so, for example, the FDA issued a pivotal medical device clinical investigations document about 2 years ago, and that goes through not just randomized clinical trials but other kinds of designs that can be used in trying to figure out -- and although that document's primarily for the PMA route, it would have potential applications for 510(k)s as well.

So thank you.

DR. HARRIS: Dr. Miller.

DR. MILLER: Thank you. Mike Miller.

Just a comment about the registries. I think I appreciate your comments about the cost and expense to make it a good registry, and I think a registry for this particular problem is way overkill and unnecessary. But looking at wound care in general, I mean, to create -- there have been some efforts by some companies. I know at Ohio State, we work with a company, and there are 120 wound centers on part of a registry. I think we heard a presentation yesterday by another Florida firm. I believe it has a registry. I mean, these things are cropping up. I think to look at the issue of wound care in general, a registry is fantastic, and it would be worth the investment. For this particular thing, I think a registry is just -- it's too much of an effort, you know.

DR. HARRIS: Ms. Lott.

MS. LOTT: Michelle Lott.

Before we get too far away from Dr. Hickerson's and Dr. Sayeed's exchange a moment ago, I want to loop back in and comment on that, particularly that Dr. Hickerson turned to Dr. Sayeed and said, oh, we're not talking about that type of dressing here. This dressing wouldn't be available in those care environments. And I think we need to back up and think because that's a possible level of stratification, is why wouldn't that type of dressing be? Is it higher risk? Is it used on different types of wounds than these others at general care levels? Because technically the solid wound dressing is a huge, even in itself, covers a huge spectrum of products. That covers a Band-Aid with Neosporin at Walgreens. That covers the type of devices that are available at these outpatient cares, and that also covers these more complex devices that Dr. Hickerson said would not be available for outpatient care or to be provided directly to patients. So I heard that there was even a level of stratification in our classification discussion in that conversation.

DR. HARRIS: Dr. Alam.

DR. ALAM: I don't have a response to that, Ms. Lott. So I don't know if FDA wants to

comment on that. I'm happy to defer.

But I was going to comment on the issue pertaining to registries, and I would agree with comments made by Dr. Miller that I think it is excessive in this context, although it might be nice for the increase in medical knowledge around wound care in general. And I would consider one problem with the registry idea, apart from the cost and the onerous burden of creating these up and managing them, what would we do with that information? If we didn't like it, would we take products off the market? Would we restrict their indications for use or their claims? I mean, I think really it essentially entails kicking the can down the road and saying we can't do anything today, let's have a registry for 10 years and then think about this again, and I'm not sure that's an optimal outcome.

DR. HARRIS: So I'd like to once again try and circle the Panel back to discussion items that are going to get us a little closer or even closer to recommendations for the FDA regarding classification. So we are looking at, as we know, three broad categories of products, a number of which -- I mean, they're quite diverse. What can we provide as some informed guidelines or recommendations? So I just want you thinking along those lines. So I think all of these comments are obviously extraordinarily useful, but I'm hoping that we can funnel that in a way that's going to lead to some conclusive commentary.

Dr. Burke.

DR. BURKE: I just think, first of all, we can't solve all wound healing of all wounds in all patients with all their comorbidities and complications. And I think that, first of all, the 510(k) criteria are excellent. I mean, in other words, the new products are presenting good data, very excellent data, and maybe we should add two more categories to that, that the product should not delay wound healing, and those are studies that probably would be animal studies, and that there is no leaching of the product in the exudate which would go to the wound, which might be an in vitro study.

And I just think that these are good criteria, and for all of these products, if there could be just some post-approval surveillance and then that information would be perhaps just given, I mean just given so people that use a particular product could look at the 2-year-later post-surveillance data just to learn if they are more toxic, there are some adverse reactions or some documented benefits such that the patients on this don't seem to ever need IV or PO antibiotics.

So because there's a huge market and we, as physicians, choose something that somehow we hear of or read about in an article that we think we will try, and if we like it, we use it again, and if we don't, when we see adverse reactions, we don't -- I mean, the market sort of -- the market and the astute physicians and nurses certainly notice if something works, particularly if it's something that's going to cost more and be more difficult somehow to educate the patient. So I think in some way, first of all, I mean, we all really care about our patients and want to see them heal, and if perchance we try something that we read about and then we see, for our own eyes, helps healing -- I mean, kind of the market shows if something is good, and if there could be maybe one or two criteria more added to the 510(k), that may or may not be necessary.

And then I think also, I just want to echo what Dr. Hunt said, that clearly catheter insertion sites are a whole different thing. It's in a healthy patient. I mean, the topical wound is healthy, and so it's a whole different category, I would think. But it could still be part of this 510(k).

DR. HARRIS: Dr. Miller.

DR. MILLER: Thank you. Mike Miller.

I think that the FRO category is too broad. I think it would make sense to break it up, and some sensible ways to break it up would be, in my mind, the intention of adding the antimicrobial. If it's to improve shelf life or maybe to open the container multiple times,

that's really a different indication than putting it on a patient and managing the wound. So I think it would make sense to split those two out in terms of the intended purpose.

I think it would make sense to split out based upon agent, if the agent used is one like a metal or like one of these others, the ammonium compounds or these sort of antiseptic things. That seems different to me than if you have an antibiotic in the thing. So I think antibiotics should be held to an extremely high set of standards to prove value because of the risk of resistance and things like that.

And I think it makes sense to break out the catheter ones, too, because when you put the dressing on a wound catheter, you're not putting it on a wound, on a central line or something. You don't really have a wound there. It's a very clean site. But if you're putting the dressing on an actual wound, that seems different to me, too. So I don't know if somewhere in there, there may be some rational way to break up FRO.

DR. HARRIS: Okay, we're going to have a final question before our lunch break.

Dr. Sood.

DR. SOOD: Geeta Sood.

It wasn't really a question, but more of a follow-up. I like the idea of subdividing the categories based partly on the risk of the additive agent. Going down the chart, it looks like if it's not life threatening but there is significant risk, then that could potentially be classified as Class III, and I think antibiotics potentially could fall into that category because of the ecologic risk, potentially other chemicals. I saw steroids was one of the chemicals that's also added. I don't know that much about steroids, so I would defer to the dermatologists and the plastic surgeons in the group about that. But I think that may be one way to subdivide it, as you were suggesting.

DR. HARRIS: Okay, we will now break for lunch. Panel members, please do not discuss the meeting topic during lunch amongst yourselves or with any other members of

the audience. We will reconvene in this room at exactly 1:15. I'll ask all Panel members to please return on time. Take any personal belongings with you at this time. The room will be secured, but you will not be allowed back until we reconvene.

Thank you.

(Whereupon, at 12:15 p.m., a lunch recess was taken.)

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

(1:15 p.m.)

DR. HARRIS: I'll call the meeting back to order. At this time I'd like to reopen the floor to the experts around the table, to continue our deliberation on any issues that you may have and/or any data that you've heard today either in the Panel presentations, the discussion with the FDA, or the material that you've read in your Panel packs.

Before we get started with that discussion, I wanted to make a couple observations. There was a list of substances that was circulated, and you should have one at each of your seats, prompted by questions, and it essentially breaks down the Appendix No. 2 into three separate groupings. The first grouping, and please correct me if I'm wrong, these are active ingredients in drugs; the second grouping are these over-the-counter consumer antiseptics, and those are eligible for over-the-counter drug review; and then a third page of those over-the-counters that are not eligible for review.

Any other comments FDA would like to make about these listings?

DR. ASHAR: Yes. This is Binita Ashar.

What we did is based on the discussions, we broke out these lists. Of course, there are many others that have not been broken out which include botanicals and, I believe, some other inactive ingredients. And there are other categories as well. But these were the three that the Panel had focused on, so these are the ones that we broke out.

DR. SHERMAN: This is Rachel Sherman.

I'll just remind everyone, and I've said it before, but if drugs are approved or under a monograph, if they're used for a different condition of use, then they may not have been studied or likely not to have been studied.

DR. HARRIS: And Dr. Elmore, you were going to make two references available to Panel members addressing animal models.

DR. ELMORE: That's correct. That's just in response to the question that you had posed earlier about the differences in wound healing between rodents and humans, and in rodents the main type of wound healing is by contraction, and in humans, it's by re-epithelialization. But in rodents, they put in a plastic stent to keep the wound open, so that's how they get around that. So it does mimic human wound healing. So I provided a couple. And for the rat, it also is the diabetic rat model, which I think you may find interesting. It may be of use to the FDA as well. But there are many, many references. So I think it would be easy to pull up not just these two but others as well. I just gave these as examples.

DR. HARRIS: And the best way to disseminate those references -- so we'll get them to Ms. Washington, and she'll give them out.

DR. ELMORE: I sent them to Evella already. She has them.

DR. HARRIS: Okay, great.

So I'd like to begin our final session of deliberations, or final afternoon of deliberations, with a reading of the Panel questions. In general, we're going to be asked to comment on the -- so we've broken it into three classifications of products we've been discussing, then discuss what we feel are the risks, the appropriate mitigations or controls, and then ultimately our recommendation for classifications. Now, there may be other recommendations we'll make, but that will be the overall structure for our discussion.

Dr. Chang, would you please read the questions?

DR. CHANG: In the previous presentation, FDA described three categories of wound dressings combined with drugs:

1. Solid wound dressings combined with drugs
2. Wound dressings combined with drugs formulated as a cream, gel, or ointment

3. Liquid wound washes combined with drugs

For the remainder of the day, you will be asked to address a set of questions for each of the three categories. As you respond to the following questions, please remember the definition of each wound dressing category.

Solid Wound Dressings Combined with Drugs: For Solid Wound Dressings combined with Drugs, FDA has identified the following risks to health based upon review of the medical literature, information available to FDA on cleared products, and the Medical Device Report databases. Please comment on whether you agree with the Potential Risks to Health presented below and identified in the overall risk assessment of these products within the product code FRO. In addition, please comment on whether any additional risks should be included in this overall risk assessment of Solid Wound Dressings combined with Drugs under the product code FRO.

Potential risks to health include:

- Adverse tissue reaction
- Delays in wound healing
- Incompatibilities with other therapies
- Increased risk of contributing to antimicrobial resistance
- Infection
- Loss of barrier function
- Microbial growth within the product
- Product degradation during storage
- Retention of dressing material in the wound

DR. HARRIS: So the questions before us are do we agree that these are the potential risks of these sorts of solid wound dressings? We could potentially delete some of these risks or recommend they be deleted or recommend others be added.

Dr. Elmore.

DR. ELMORE: I'm just wondering if anyone thinks that hypersensitivity should be added to the list.

DR. HARRIS: Dr. Sayeed.

DR. SAYEED: Yes, I agree.

DR. ELMORE: Oh, I'm sorry.

DR. HARRIS: I think that's -- yeah.

DR. ELMORE: I apologize, it's there.

DR. HARRIS: Okay.

DR. SAYEED: In terms of not just local reaction, though, systemic reaction.

DR. HARRIS: Dr. Sood.

DR. SOOD: Could you clarify infection? What do you mean by infection in this scenario?

DR. CHANG: So an infection could result from a number of different causes, which might be how it's used, the material in the product, or from any other, I guess, causes. It's really infection of the patient and the wound.

DR. HARRIS: Ms. Lott.

MS. LOTT: Michelle Lott.

I've just got a general comment before we start diving too deeply into the scientific matters. I don't know if the rest of the Panel, how familiar they are with the concept of least burdensome. And so, ultimately, the statutes and recommendations that FDA develops out of this have to follow the least burdensome approach, which means what is the minimum amount of scientific data that they have to have for safety and effectiveness? So maybe if the Panel could keep in mind that, hey, this is what we absolutely have to have to be able to demonstrate these claims, to mitigate these risks, and but this is what we

would like to see, maybe, in a best case to give some weight or prioritization to the recommendations.

DR. HARRIS: Dr. Alam.

DR. ALAM: Hi. Murad Alam.

In looking at these lists of risks, I think it's important to also note the modifier, which is potential risk to health. And I think, as we're going through this, it will be helpful to not only consider the potential risks or the theoretic risks, but the ones that have been demonstrated in all or some of these products at some reasonable likelihood of occurrence. So I think, at least from my standpoint, it would help me. We might not have additional information. I know we have received all the adverse event information, and you've already shared that with us. But I think there is a big difference, when you're regulating something, to consider the potential risks and the risks that have actually been known to happen in abundance or even infrequently.

DR. SHERMAN: We're just having an internal discussion electronically here, and I think the whole team would like -- you've been thinking about this all the time, but just to remind you that one risk is lack of evidence, and how does one mitigate that risk? If you keep that in the forefront of your minds.

Thank you.

DR. HARRIS: So I have a question, Dr. Chang. Listed under the potential risks to health, if a substance is actually absorbed and can be documented to become systemically distributed, is that potential risk listed anywhere here or contained under any of these headings?

DR. CHANG: I'll take the example of a degradable suture. We do have methods for evaluating systemic toxicity of absorbed materials into the body, and that would be captured under the risk of adverse tissue reaction, including toxicity. For materials that

may become systemically available, there are standard methods for evaluating that under systemic toxicity and a set of biocompatibility standards.

DR. HARRIS: And so for the various -- I guess this is a point of clarification. So these are categories of potential risks, but speaking to a comment just earlier, are we assuming that every solid dressing would have all of these various types of risks interrogated, or would it be is this more like a menu from which you would select which are specifically appropriate for one dressing type versus another?

DR. ASHAR: This is Binita Ashar.

If I could step in here, I think a first step in this process is identifying the associated risks, you know, where we know that there is risk, and then the second step is going to be understanding how those risks can be mitigated. So just flipping ahead, there's a list of potential mitigations that we've also proposed.

If the Panel is concerned about systemic absorption, you can specifically call that out. You know, although adverse tissue reaction may entail part of that assessment, if that is of concern to you, then you can specifically state what you'd like to see or what risk you're concerned about, and then you can deliberately go on to talk about the risk mitigations for that.

DR. HARRIS: Dr. Hickerson.

DR. HICKERSON: Bill Hickerson.

If you're going to look at the absorption, do you have to look at the amount of absorption that you would have a concern with?

DR. ASHAR: I think that would be one way that you could approach it from a risk mitigation perspective. So the risk is absorption, and the risk mitigations could be, you know, establishing parameters by which there would be an acceptable benefit/risk profile.

DR. SHERMAN: Perhaps there's a level just that you would want the systemic levels

quantified to prove there was absorption, there was not absorption, or there was absorption at an acceptable level. One could think about lidocaine, for example, in that category.

DR. HARRIS: Ms. Lott.

MS. LOTT: Would leachability potentially be an inverse factor to the level of absorption? Like if the manufacturer could demonstrate that the material does not -- the antimicrobial does not leach out of the dressing, do they on the inverse need to do, then, absorption studies?

DR. HARRIS: I mean, certainly I know, for medical devices that are coated, there are in vitro assays for looking at the solubility of that coating. But whether or not -- I think that would ultimately be FDA's determination as to whether that could substitute for systemic absorption tests or pharmacokinetics.

DR. ASHAR: So again, going back, the risk is systemic toxicity. When you're discussing risk mitigations, there could be any number of ways that that risk could be mitigated. And so when you get to that point, you could discuss some of the ways that FDA could consider having that risk mitigated.

DR. ALAM: Along those lines, you referred to the lidocaine levels for, I suspect, topical lidocaine preparations. For many or most of these chemical additives and/or drugs that might be under monograph but are not being delivered in the same way in these combination products, do we actually have data regarding the maximum safe plasma levels or anything comparable? Or would that need to be then ascertained by animal studies or some other toxicology methods, if in fact we were going to check levels to make sure they were below a relevant threshold?

DR. SHERMAN: Well, I picked on lidocaine because there's an FDA order not to put it on intact skin. So one wonders how one should extend that to non-intact skin. So to

Ms. Lott's point, perhaps -- I mean, your advice might be that in an in vitro assay showing that none leached would be sufficient, or perhaps an animal model or whatever your considerations might be. Similarly, you might advise us on other types of steroids -- yeah, systemic absorption steroids and then, of course, absorptions of the antimicrobials. So you're correct, but I think it would be a stretch to tell you we know what the acceptable level is of lidocaine, for example.

DR. HARRIS: Dr. Elmore.

DR. ELMORE: This is semantics and just about the terms "allergic reaction" and "sensitization." Sensitization has different meanings, so I think it might be more appropriate to say topical or systemic allergic reaction and remove the word "sensitization."

DR. HARRIS: What specifically does sensitization refer to that --

DR. ELMORE: It can have different meanings. So it can mean, in some cases, the repeated exposure to something which will then result in an allergic reaction. But it can also -- so I'm saying that it's not just that. It can also just be the first initial contact with something, which can be an allergic reaction. So I think, in this case, it was meant to be topical allergic reaction. So I think we can take the ambiguity out of that by not using that word "sensitization."

DR. HARRIS: But would not people potentially be at risk for sensitization as well?

DR. ELMORE: Yes, but if you said topical allergic reaction, that would cover that.

DR. HARRIS: Oh.

DR. ELMORE: That's just a broad term.

DR. HARRIS: I see.

DR. ELMORE: So it's sort of all encompassing.

DR. HARRIS: I got you. Okay.

Dr. Sayeed.

DR. SAYEED: In terms of toxicity, the FDA could also look at other organizations within the government, like the EPA. OSHA has permissible exposure limits, and ACGIH has threshold limit values, so those may be useful.

DR. HARRIS: Dr. Reller.

DR. RELLER: Barth Reller.

I'd like to ask Dr. Sherman and Dr. -- for clarification. These three lists that were handed out, is it correct that in the aggregate they include all of the putative active agents in the compounds? I mean, the PROs under discussion?

And the second part of that is that the compounds that are under OTC eligible and then ineligible, are those compounds that have come under scrutiny by CDER that are also perhaps different concentrations in the products under discussion? Is that the correct parsing of these three tables?

DR. ASHAR: Yes, I believe so. The list is much more comprehensive than those three tables that we've provided, but the first list is active ingredients in drugs.

DR. RELLER: Right.

DR. ASHAR: There are many other chemicals that are present that are not --

DR. RELLER: Sure. But these are the putative active ingredients that would -- okay, thanks.

DR. ASHAR: Yes.

DR. HARRIS: Dr. Miller.

DR. MILLER: Yes. I think if we're going to be complete, if we're going to show concern about absorption of the agent, then we should also look at absorption of the degradation products of the agent that may happen in the dressing as well. You mentioned steroids. I don't know whether steroids should be included in this grouping because the dressing is not going to respond to the steroid. The steroid, if you're going to put it in the

dressing, it's going to be an interactive dressing. So that should be pulled out of this grouping, I think.

DR. SHERMAN: That's the kind of feedback we need to hear from you because, as you've all pointed out, it's a very broad grouping, over 700 of them. So if you feel there's some that should be pulled out -- and obviously, we mentioned ones that struck us as notable -- then we need to hear that from you.

DR. HARRIS: Dr. Alam.

DR. ALAM: On the topic of steroids, I don't want to comment so much on whether they should be pulled out or not. I think that's probably a bigger question. But with regard to risk, since we've brought that up, topical steroids, I think Dr. Burke and I, by virtue of being dermatologists, probably use a fair quantity of topical steroids as therapeutic agents. And at least from a toxicity standpoint, I would not be very worried because we routinely use Level 1 fluorinated topical corticosteroids, even on non-intact skin such as, for instance, after full-face resurfacing and so forth, and there's really no systemic toxicity that's usually associated with that, nor is there significant local toxicity.

So I would really not be worried about that because, even with very strong steroids that are specifically applied on open wounds, that doesn't seem to happen in the vast majority of cases. And here, I'm suspecting whatever amounts are present in some of these products are probably sub-pharmacologic or very low doses.

DR. SHERMAN: If you know of evidence that would help us understand how that's been studied, and for example, in terms of adrenal suppression, that would be very helpful.

DR. MILLER: It's Mike Miller again.

If I could just comment to that. I mean, what our dermatology colleague says is exactly true, but it's not really relevant because we're talking about, you know, delivering a drug topically, and these devices aren't supposed to deliver anything topically. They're

supposed to just treat the dressing. So they're really very different, and they should be treated differently, even though while everything he said is true in principle, it's mixing up these things a little bit.

DR. HARRIS: Dr. Reller.

DR. RELLER: Barth Reller.

On the other hand, with the facility absorption of the various steroid compounds under an occlusive dressing, is the absorption greater, and are there some corticosteroid compounds, if used in a sufficient concentration under an occlusive dressing, that have the potential for systemic absorption that would have potential clinical adverse effects? And I'm thinking of, as I remember MyMeds app, in the dermatology component, the most potent used -- and correct me -- is clobetasol. And if you use enough of that under an occlusive dressing, not that it's included on the list, can you, over a period of time, have physiologic or un-physiologic effects on the axis?

DR. BURKE: The answer is yes. But for topical clobetasol -- and you're correct that under occlusion more is absorbed. I mean, you mostly get skin atrophy and telangiectasia. The time we worry about adrenal suppression is in burn patients that have a large surface area and there's maximal absorption, or in children with atopic dermatitis. So we worry a lot in children, and the younger they are, the more we would try not to use a strong steroid. But those are the only cases, I think, that we really know of that adrenal suppression has been measured.

DR. ALAM: Just as a follow-up on that -- and I commend you for how you phrased that question, Dr. Reller, because I think you missed your calling as a lawyer --

(Laughter.)

DR. ALAM: -- since we all have to say yes to that. But I mean, I think there were a lot of hypotheticals. If it's a super-potent steroid, if it's in very large quantities, if it's under

occlusion for some indeterminate amount of time, could it ever happen? Well, certainly it could, but I suspect that's true of most of the substances we're looking at. If we had those, you know, enormous concentrations for very large periods of time, it could happen. But I think, and leaving aside cases where this would be applied, a wound dressing would be applied to a substantial fraction of a person's body surface area, and they were debilitated somehow before it was done, I suspect it probably wouldn't be functionally a problem, a although I certainly agree with Dr. Miller that the fact that it wouldn't hurt somebody isn't really getting to the issue of whether something that potentially has a therapeutic effect on the skin should be included in a combination product and approved through this pathway.

DR. HARRIS: Dr. Sood.

DR. SOOD: To follow up on Dr. Burke's point, the children or age grouping, I think, would be significant because there are a lot of elements on this list that would be not so important or significant in adults but are very different in children and newborns, like chlorhexidine and other medicines and ions as well.

DR. ALAM: If I may. Murad Alam.

I agree with you, and I think that's a good point, and I know that our pediatric dermatology colleagues tend to be much more conservative about the use of some of these products on a routine basis in children. So it's certainly one thing that FDA could consider, that if there was some change in labeling or some issues pertaining to how to convey the risks, that maybe they should consider children separately.

DR. HARRIS: So there has been some discussion about perhaps adding to this list systemic absorption or some terminology to reflect that, and perhaps clarifying terminology regarding systemic versus topical allergy -- or not sensitization, but toxicity. So if there are no other comments about this list of potential risks for solid wound dressings -- oh, Ms. Lott.

MS. LOTT: Well, just now that we're kind of exchanging the term "pediatric" back and forth, out of curiosity, what is the Panel's definition of pediatric? Dr. Alam?

DR. BURKE: It depends on the medication. I mean, most medications specify not to be used if an infant is less than 2 months old or a child less than 2 years old. They're the usual cutoffs. But that would be in the package insert of each particular medicine, so it varies.

DR. ALAM: It's Murad Alam.

And I'm not suggesting that that's necessary. I'm just saying that it's a potential thing that could be explored further. And it might not be valid, but I do think there is a distinction that sometimes is raised along those lines, but it might not be relevant.

MS. LOTT: I just want to make sure we have vernacular alignment because there are FDA guidance documents that define a pediatric population as 18 or younger, and I think that that's a little bit beyond the scope of what you guys are intending in your conversation.

DR. HARRIS: Okay, Dr. Chang, if you could please now read the mitigations or controls.

DR. CHANG: For Solid Wound Dressings combined with Drugs, the risk/mitigation table below outlines the identified risks to health and potential regulatory controls or data requirements that FDA could apply for each identified risk. Please discuss each of these potential controls and whether it, either alone or in combination with others, adequately mitigates the identified risk.

DR. HARRIS: Comments from the Panel?

Dr. Sayeed.

DR. SAYEED: I just want to reiterate my concerns over labeling; I think if we're going to label products, that there is some utility from it.

DR. HARRIS: Dr. Miller.

DR. MILLER: Is there a similar list like this for solid wound dressings without drugs?

DR. CHANG: In the classification discussions for the Class I wound dressings, I believe that similar risks were discussed, as well as mitigations, but I do not know if we have those available right now.

MS. LOTT: But if it's Class I -- excuse me, I'm sorry. Michelle Lott.

If it's Class I, it wouldn't have a special controls guidance document, so there wouldn't have been that discussion, correct? Or do Class I products sometimes have --

DR. ASHAR: Right.

MS. LOTT: -- special controls?

DR. ASHAR: This is Binita Ashar.

Yes, Class I products have the general controls. There is only one wound dressing that's Class II, and that's pDADMAC that you referred to before. And then there is one that is regulated by CDRH that's a Class III product.

DR. HARRIS: So I interpret that to mean no, there are not.

(Laughter.)

DR. HARRIS: Dr. Sayeed.

DR. SAYEED: One thing that we could consider adding, not just to solids but to the rest of these wounds, are what Dr. Campbell had referred to, is clinical studies in our -- you know, if we end up labeling these as Class II and maybe putting a time frame on them as well.

DR. HARRIS: Can you clarify exactly that comment, meaning that we would want manufacturers or practitioners to conduct trials or to contribute data to a registry or what?

DR. SAYEED: That's an excellent question, and that's probably something the FDA should answer, but probably a combination of FDA and manufacturer input in terms of the type of study, the study design, those types of aspects.

Dr. Campbell, I'm not sure if you want to weigh in.

DR. HARRIS: So I'm clear, you're referring to postmarketing?

(Off microphone response.)

DR. HARRIS: Okay. Dr. Campbell, do you have any weight on that question?

DR. CAMPBELL: No, not really. I guess the only place it would fit here would be perhaps in vivo evaluation, where in vivo could be animal studies, but it could also be human studies. So I don't know if that's quite what you meant.

DR. HARRIS: Dr. Hunt.

DR. HUNT: I just had a question about the labeling, just for clarification. So this is labeling that the manufacturer would provide to the FDA, and then the FDA would modify it, or is there standard labeling language that's used for these types of things that would be given to the manufacturer that would then be modified according to their product? So how does that work?

DR. ASHAR: This is Binita Ashar.

So as we've identified -- or the Panel, rather, has identified the various risks; now you're at a place where you're proposing mitigations to address the risks. So with respect to labeling, it would be helpful for us to know what you would like to have communicated in the labeling regarding these products so that we could work with manufacturers to ensure that those issues are addressed. Likewise, with clinical studies as a risk mitigation measure, whether -- I guess what you're proposing is having them done in the postmarket. There are a couple of things to keep in mind.

First of all, it would be helpful to know what the clinical study is designed to do and what risks it's designed to address as a mitigation measure. And the second thing to keep in mind is the overarching concept that, in the premarket, we assess the product and assure, you know, and evaluate its safety and effectiveness before allowing approval or marketing

clearance for a specific product. So the postmarket is not intended to be a mechanism by which we are delaying our assessment of safety and effectiveness. That's supposed to be done in the premarket.

DR. HARRIS: Dr. Sayeed.

DR. SAYEED: So just to clarify a point for myself, so because these products are already on the market, all of our studies would be postmarket studies, correct?

DR. SHERMAN: Yes and no. Remember that these products are on the market, but if and when they are classified, then they can serve as the --

(Off microphone comment.)

DR. SHERMAN: Thank you. Sorry, I am a drug person. For substantially equivalent determination, those new products -- and some of them would then have to do it premarket. So we're developing a new regulatory paradigm. But you're correct, currently what's on the market would not be pulled off pending the --

DR. HARRIS: You had a follow-on question?

DR. SAYEED: So then we're talking about Class III, because if it's a premarket analysis, it would be a Class III device.

DR. SHERMAN: Well --

DR. SAYEED: Is that correct?

DR. SHERMAN: -- that gets to Dr. Ashar's point about what kind of clinical studies you're asking us for. So, for example, if it was a limited study -- PK comes to mind or it could be something else. So not to, right, establish safety and efficacy.

Go ahead.

DR. ASHAR: I think that what it really boils down to is that if we cannot write special controls that could serve to bucket a group of devices, that we don't feel that we're going to adequately be able to mitigate risk by establishing special controls, then strong

consideration then goes to the Class III classification where we're going to need to establish safety and effectiveness for an individual product based on its own evidence, because each product may be, in some circumstances, so unique that it's not possible to establish special controls that would serve as the precedent for other devices that may come afterwards. Each device is going to need its own dataset from which it is based on, the safety and effectiveness is based on.

DR. HARRIS: Ms. Lott.

MS. LOTT: I just want to clarify that just because a product may require a study of some sort does not necessarily require it to be Class III. There are about 10% of 510(k)s that are currently approved that have got some sort of study data in them. And correct me if I'm wrong about this number, but isn't there something called a 522 study or some other? Or is that for postmarket?

DR. CHANG: I believe that is --

MS. LOTT: Postmarket. But there is a mechanism for FDA to request a postmarket study within a 510(k). And it's also possible, if the company doesn't do a study up front, for FDA to specifically request a study during the review of a 510(k). So I don't want to -- I want to make sure our conversations don't immediately go through link, study, Class III.

DR. HARRIS: Dr. Alam.

DR. ALAM: Just looking at this list of identified risks and possible mitigation measures, I have a question about the last one, which says retention of dressing material in wound, and the potential mitigation is labeling. In that case, would labeling explain to the user perhaps, or the patient, how to avoid retention, or is there some additional mitigation that would be done to assess whether retention was a routine outcome of using this material? Do you see the distinction there between instruction versus testing?

DR. CHANG: Yes. So the potential mitigation measure presented is for labeling to

state that the clinician should count the number of pieces of dressing materials to make sure that none are inadvertently left behind, as may sometimes happen and may be a risk. You bring up the potential for other risks related to retention of dressing material in the wound, and perhaps there are other mitigation measures that may be appropriate.

DR. HARRIS: I'd just like to follow up on that question. So the idea that a practitioner might leave behind grossly visible segments of a dressing, I think, are less concerning to me. What's more concerning to me is that there might be microscopic fragments of a dressing left behind that would not be readily visible, and at some point it would seem to me potentially a grounds for disqualification as a dressing if it's disintegrating during the process of its use. So how is that -- is that an issue that is being potentially mitigated here? Certainly not by labeling.

DR. CHANG: Are you suggesting that perhaps bench, animal, or clinical testing would be appropriate for that risk?

DR. HARRIS: I think my personal opinion would be yes. If there is concern that the dressing itself might fragment or disintegrate during its use, I think there should be some testing made to then limit the length or duration of its use such that that would not be a routine problem.

DR. ASHAR: Dr. Harris, I think you raise an excellent point. So what you're talking about is retained fragments of the dressing being in the wound that could potentially have clinical ramifications affecting wound healing, and that is a question that we do ask. If you would like for us to more explicitly -- you know, I believe what currently is being done is that there's animal testing that's assessing wound healing in such circumstances that's being performed. But if there are other things that we should be doing around that issue, then we'd like your feedback.

With respect to labeling on this issue, I think what Dr. Chang stated is correct. You

know, if there's information that we need to do to alert providers that -- manufacturers need to do to alert providers that this could happen, how to prevent it from happening, what to look for if it does happen, things along those lines in the labeling is what we were getting at here.

DR. HARRIS: Just one second. So at least one way that I have been trying to organize my thinking here is that we have components of the dressing and things that are included to impact the dressing, and we're talking about how they may, in a potentially -- in an actually stated unintended way, impact the wound, whether it be through a biochemical or physical property of that dressing. So it would seem to me that anytime there is a concern that that is happening, that there are these unintended consequences of using a dressing, that that then has to be examined in some way to then determine that that unintended event is not going to be harmful to the patient.

DR. ASHAR: I think you've stated it very well. And in addition, the only thing I would add is that as you are discussing the potential mitigation measures, that those mitigation measures be grounded in some evidence that assures us that the product would be safe and effective.

DR. HARRIS: Dr. Hunt.

DR. HUNT: I just have a question with respect to that, comparing it with wound dressings without drugs. And so what you're saying is that maybe the drug, in and of itself, would cause it to leave fragments in the wound as opposed to just standard dressings, which we know do fracture and come apart as we're trying to take them off of wounds. So it seems like if that is the question, then you almost have to do some type of mechanical study, like was mentioned earlier, with suture material or some type of -- you know, you could potentially do in vitro studies with different moistures, depending on how moist a wound is or something like that. But I would think that should be something that would be

easy to answer with just in vitro bench work kind of studies.

DR. HARRIS: Ms. De Luca.

DR. DE LUCA: Dr. Harris, could we do something sort of similar, call the average owner of a rat factory in Wilmington, Mass and ask them where their rats and mice go and what the procedures are being called for, because they specifically asked for specific animal models? We could just save a lot of doing the hard work when it's been done and they probably have the figures.

DR. HARRIS: Um-hum. Are you saying specifically that someone would have already examined the interaction between these dressings and wounds in animals?

DR. DE LUCA: Yes.

DR. HARRIS: It's possible, sure.

Ms. Lott.

MS. LOTT: I think Dr. Hunt brings up a great point. You know, when we are discussing these things, there are an entire set of wound dressings that are Class I devices that don't have drugs in them and that could very easily contain the same risks. But because they're Class I, they're under general controls and aren't subject to that same rigor. Are we wanting to add that rigor to this product just because it contains an antimicrobial, and the antimicrobial, in itself, doesn't change the risk that is shared with the Class I device?

DR. HARRIS: Well, that you don't know. That's a large assumption. And I think it was pointed out earlier that if you're going to make combinations, you have to look at the combination rather than looking at the individual contributions as if they're isolated, to be certain.

Dr. Sayeed.

DR. SAYEED: One other thing that I was just thinking about was even with, let's say,

the metal dressings and the non-antimicrobial dressings, you know, in terms of toxicity we should really be considering the amount of systemic uptake of some of these things because, as nanoparticulate research is getting higher and higher and more evolved, we are noticing that there are toxicology profiles to certain materials.

DR. HARRIS: Dr. Reller.

DR. RELLER: Barth Reller.

Recognizing that the entire list is large and heterogeneous, that it's formidable, perhaps impossible to get into all the nuances of all of the different options, to me, in balancing the risk and benefit and addressing the special controls, there are three large categories that are of particular interest, it seems to me. One is those drugs that risk is principally owing to, not exclusively, but principally owing to toxicity, for example, lidocaine, and a subset of that absorption component is sensitization or allergy. And it would seem that on that issue, the special control could be as listed, or if not listed, of actually measuring whether material is absorbed, okay?

The second category, and a big one that includes perhaps more agents, would be the affect on wound healing, so the hypochlorite, the hydrogen peroxide. And this could be done in the animal models. It was discussed earlier that in order to -- because what we're discussing is whether agents in Category II should be moved to III or conceivably down to I.

So, for example, if hydrogen peroxide, just as a theoretical example, delayed wound healing or didn't show one way or the other in an animal model, that one could conceivably either take it out and downgrade the base product to I, or if it actually delayed wound healing, that probably wouldn't stay on the market anyway. But, you know, some of these other factors that are important, this is where I think use would dictate it. For example, if one of these products doesn't keep the wound moist and moisture is important, I think people are not going to keep using it if it doesn't keep the wound moist.

And then the third category -- and I think all of these compounds, some of them may include more than one category, conceivably -- is the matter of antimicrobial resistance in a more narrow sense of antibiotic resistance, either directly because it's an antibiotic that's in the combination product or it is an inert compound not used as a therapeutic antimicrobial agent but it stimulates selection or plasmid that may carry collateral damage.

And it seems to me those three categories, special controls such as the absorption studies, the effect on wound healing in an animal model may be adequate. And then there are others that -- and specifically, antimicrobial resistance, given its increasing importance. For example, Dr. Patel mentioned earlier polymyxin, and others have. There are some organisms that even though it went out of practical usage existence when there were better things that came along, you know, it's come back because there isn't anything else available. No matter how poor it is, it's still better than nothing when you're really up against it.

So it seems to me that not trying to tackle everything but to categorize things, and it may be -- some of them may be in one additional category, and some of the controls would take care of it, and it may come down to two, three, four, five compounds, that the only thing that gives a sufficient assurance level of the risk-benefit analysis is a clinical trial maybe.

DR. HARRIS: Dr. Miller, then Dr. Burke.

DR. MILLER: This is Mike Miller.

I would add the labeling to the mitigating measures for loss of barrier function because the barrier function is going to be dependent on proper application. So I think some instructions of how to do that properly is appropriate.

DR. HARRIS: Dr. Burke.

DR. BURKE: So I agree with Dr. Reller. I mean, if just to the 510(k) you add leaching,

which would lead to possible leaching from the bandage into the wound, which could lead to toxicity -- and he mentioned if wound healing is delayed. And then the third, antibiotic resistance, which is tough to test, but then you could have tensile strength and stability of the solid matrix in the presence of the second, of the drug, and that's very easy to test.

DR. HARRIS: I just have a general question for anyone who is knowledgeable in this area. Are there animal models that can effectively predict the induction or propagation of antibiotic resistance or antimicrobial resistance?

DR. PATEL: No, I don't think there's any animal model that's validated for predicating antimicrobial resistance. It's actually a very tough thing to evaluate because not only are -- you know, you have to be concerned about new resistance that has not previously been detected, and then also existing resistance, and then the linkage of existing resistance to other resistance genes, which I think are all questions that extend well beyond an animal model.

DR. HARRIS: They may extend beyond a clinical model. So I have a question because I was curious. Dr. Reller, does that influence your thinking regarding that third category of concern? If you had that concern, would you then suggest that those be classified as Class III devices or combination products?

DR. RELLER: Barth Reller.

Well, the absence of a special control such as animal studies for this particular adverse effect, I think, does influence me, and it's probably apparent from my remarks, is unless it's shown to add something, I cannot comprehend, on those agents that are used therapeutically certainly, and possibly the ones where the resistance is collateral damage, we don't want to use them in animals and we don't want to use them in soaps, not that they are in soaps, I realize that. But if it's not doing something really important or it's just there and there's no benefit at all, then I don't think there should be any risk. And the only

way to have no risk is to remove them unless they're shown to be important.

DR. HARRIS: Dr. Sood.

DR. SOOD: I would agree that antibiotics, specifically antibiotics that are used as therapeutic agents, probably as a clinician and epidemiologist, I would want to see clinical data before saying that that would be okay. The antiseptics, I think there are a lot of antiseptics that are being used relatively broadly, like chlorhexidine, etc. So in my mind, I would categorize that as a slightly lower risk of resistance.

DR. HARRIS: Dr. Patel, then Dr. Alam.

DR. PATEL: So I would just want to modify this to the antiseptics where there is plasmid-mediated resistance. I think that increases the risk, such that you would want to have clinical effectiveness data before that is being used.

DR. HARRIS: Dr. Alam.

DR. ALAM: I don't want to beat a dead or wounded horse, I guess, no pun intended, but I think we also have to stay focused on how many of these adverse events we've really seen versus a hypothetical. For instance, if you sort of say, well, even antiseptics, we're not going to allow them, keep in mind antiseptics are ubiquitous in the world. And so it's not going to be that much harder for someone to tell their patient why don't you get this antiseptic, then you can put that on your wound, and then you can stick on this dressing that doesn't have the antiseptic in it.

So unless we're planning on saying antiseptics are now all going to be controlled products which only certain people can get for specific indications, I think we have to accept the fact that unless they're doing something worse in the dressing than they're doing in nature, in general, we should be cognizant of the fact that they're ubiquitous and maybe not excessively restrict their use.

DR. HARRIS: Dr. Hickerson.

DR. HICKERSON: I think that you were mentioning the plasmid aspect, and I think earlier you mentioned silver. I think that that would be one. You've got colloidal silver that anybody can get by going into many different stores, and the aspect of having no known problem with that and the benefit that we have in the burn world outweighing that at this time, I think, comes into heavy play with what we're discussing.

DR. HARRIS: I just want to comment that all silver is not the same. And so colloidal silver is very different than silver-containing compounds, which sort of are predominantly used as the ointments or Silvadene, Silvadiazin, silver nitrate, as opposed to the silver-containing or impregnated dressings, as opposed to nano-silver containing fabrics or materials. So I think that if you're actually going to start -- you have to kind of parse silver according to its form and not in any blanket category.

DR. HICKERSON: No, I agree with you wholeheartedly on that. And it ends up becoming the release or whatever that you have that's in that dressing.

DR. HARRIS: Dr. Reller.

DR. RELLER: Just briefly. Part of the discussion has been evidenced, and when evidence has been obtained -- and it's been mentioned earlier that some of the longstanding practices in medicine have been debunked. On the other hand, one of the key elements in evidence-based practice is the best available evidence, but the second component is experience.

And this is in support of Dr. Hickerson's comment of compounds that experienced clinicians have used and believe effective that are commonly in practice. I think we need to be pretty careful about putting undue restrictions on something that is plausibly active. And I'm not trying to lump, for example, all silver, but there are some studies supporting some silver compounds, at least in our background documents that we read. So I mean, you know, it's like clinical -- this is a judgment call on these matters, and I think experience

is a very important component of clinical practice.

DR. HARRIS: Dr. Miller.

DR. MILLER: Yes, thank you. Mike Miller.

Just to put some perspective on the issue of impaired wound healing, I mean, if we use any of these things like silver or the oxidative -- oxidators, it's going to impair wound healing because they are indiscriminate in their effect on cells and everything. But it's a tradeoff between which is a bigger threat to your healed wound, the agent you're putting in the dressing or the bacteria that are in the wound.

I mean, when I use these things, it's because the bacteria are a far greater threat, and the dressing has an objectionable odor. But the idea is that these aren't supposed to get into the wound. So I mean, impaired wound healing has got to become a theoretical thing because they're not getting in the wound anyway if they're properly designed and that type of thing. This is a dressing treatment, not a wound treatment, you know.

DR. HARRIS: Dr. Ashar.

DR. ASHAR: Yeah, I just had one comment. The Panel's been discussing the risks and the potential mitigations. Dr. Sherman pointed out to me that perhaps some consideration to -- you know, in terms of silver, carving out a population. For example, for burns, the risks and the mitigations may be appropriate, but for other populations it may not be. It might be useful for the Panel to consider.

DR. SHERMAN: And if I could just follow up on Dr. Miller's comment. Two points: One, repeatedly over the last couple of days, patient-oriented outcomes, so patient-reported outcomes, such as odor, has been mentioned. That's something you could tell us that you feel that is a benefit that we could either have measured or there's evidence. So that point, I agree with you. The plan that we -- we're wondering, we're asking you, do we know? The claims are to treat the dressing. Do we know that's what's happening? That, I

think, is an open question for you to discuss.

DR. HARRIS: I'll also just point out that we've heard comments earlier about the marketplace kind of dictating practice and practitioners doing things that work for them, and I think we all know that basing our treatment of the next patient based upon the results of our last patient is a notoriously error-prone approach to practicing medicine.

And I'd also say that there are clearly numerous examples where there is an overwhelming compulsion to conform to the current standard, and there may be an opportunity here to challenge what are the current thoughts and approaches and in that way find the next *H. pylori* or, you know, abandon leeches, all of which at some point a panel like this would have been roundly endorsing.

Dr. Sayeed.

DR. SAYEED: I couldn't agree more. You know, one thing I was thinking about -- although from your experience and from what you're saying today, it sounds like silver clinically may be a benign product, but we don't know the dose of the silver in these wound dressings. We don't know how much is toxic and how much is more to protect the dressing. One thing that a clinical study would do is help tease some of these points out.

And just to go back to what Dr. Sherman was talking about in terms of outcomes, one thing that the FDA could also look at is quality adjusted life-years. And, in fact, if these dressings are improving morbidity in the long term -- or are we just healing a wound just to have patients have the same mortality? Are we -- is there any effect?

DR. HARRIS: So why don't we turn to the third element of our discussion under this category. Dr. Chang.

DR. CHANG: Section 513 of the Food, Drug, and Cosmetic Act states that a device is Class III if:

- insufficient information exists to determine that general controls are sufficient to

provide reasonable assurance of its safety and effectiveness AND insufficient information exists to determine that application of special controls would provide such assurance, AND

- the device is life supporting or life sustaining, or for a use which is of substantial importance in preventing impairment of human health, or 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
        - the device 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 impairment of human health, AND
        - it does not present a potential unreasonable risk of illness or injury.

DR. HARRIS: So now we're addressing the meat of the issue when it comes to the

solid wound dressings. I would just propose that maybe you comment on types or subcategories of these dressings that you feel should not be Class II. It's just a way of kind of honing our discussion.

Dr. Sayeed.

DR. SAYEED: I would say the indwelling catheters would be the only one that could be Class II. Based on the definition of Class III, there's insufficient information to determine that general controls are sufficient to provide -- there's no information on the rest of the devices.

DR. HARRIS: Ms. Lott.

MS. LOTT: That definition goes on to weigh the risk and benefits, and Class III is for high risk versus moderate to low risk. So does the Panel believe that these are of significantly high enough risk to warrant Class III over Class II? There are two parts to that definition, not just enough evidence, but enough risk.

DR. HARRIS: And I'm just curious. It seems like we're actually weighing the risk versus benefit. And so, as I've heard earlier, people made the comments that if the benefit is low, then the tolerance level for risk is low, that it doesn't have to be a high risk alone to be a Class III, but I don't know if that's the correct interpretation or not.

MS. LOTT: And also to Dr. Alam's point. We haven't really had a significant discussion about benefit. You know, do we have an unfairly weighted scale at the moment?

DR. HARRIS: Any other comments?

Dr. Holmes.

DR. HOLMES: I'm unclear what Dr. Sayeed just said. Can you repeat that?

DR. SAYEED: Not verbatim, but --

(Laughter.)

DR. SAYEED: So here under Section 513, insufficient information exists to determine

that general controls are sufficient to provide reasonable assurance of its safety and effectiveness. And then there is a risk. I mean, we'd been talking about antimicrobial resistance yesterday. So I mean, that's a fairly large risk.

DR. HOLMES: So you're suggesting that all of these should be Class III except, you said, the dressings that would cover vascular catheters; is that what I'm hearing?

DR. SAYEED: Based on the definition.

DR. HOLMES: Okay. Well, I couldn't disagree more. I would consider the dressings that cover vascular catheters to be a Class I device and the rest of them Class II with a possible exception of the dressings that involve hydrocortisone. I think in that instance I would tend to lean towards potentially making that a Class III.

DR. HARRIS: Dr. Alam.

DR. ALAM: With regard to Dr. Sayeed's comment, the comment that general controls are sufficient to provide reasonable assurance of the safety and effectiveness, and if that isn't met, that would only exclude it from Class I, because you could still implement special controls, so I would agree with you that most of these probably shouldn't be Class I, but I would concur with Dr. Holmes that I think most of these could be Class II with special controls.

And I don't think there's a preponderance of evidence, to Dr. Lott's point, that we have seen that suggest that even though these devices might not have tremendous benefits -- we haven't really discussed the benefits much, but even assuming -- conceding that they might not have tremendous demonstrated benefits, they also don't have tremendous demonstrated risks. The risk level is low, and the two levels are, at worst, commensurate. So I don't think we have to worry that these are either a high-risk device or devices where the risk far exceeds the benefit, and for that reason we don't need to consider Class III.

With regard to the hydrocortisone, I see where Dr. Holmes is coming from in terms

of potentially considering that to be Class III if there was a combination product that included them. I think that would be predicated, however, on the expectation that the hydrocortisone that was included with such a product actually had a therapeutic benefit. If it's in some trace amount, then it might not be relevant.

DR. HARRIS: Dr. Burke.

DR. BURKE: I also agree with Dr. Holmes. And again, I think that the 510(k) specifications are very good if we add the three things suggested: does it leach, does this product inhibit wound healing, and third, the tensile strength of a solid matrix with the drug added. And so maybe because everything that still would be Class II, the submission would have to -- has to do with the 510(k) listing, which are very good criteria. And I think that the toxicity and the resistance is very low. I mean, it's difficult to prove resistance, but we certainly know that the skin irritation is basically low. And the skin is very often the adhesive of the bandage, which is something we routinely can patch test for in patients that we expect a contact allergy.

DR. HARRIS: I have just a point of clarification and then we'll go to Dr. Sood. For FDA, so if the Panel were generally suggesting that in the absence of demonstrated significant leaching of a compound from a dressing and that it had structural integrity, that they should be classified -- and those would be special controls under a Class II device. For those products that are already approved, would they need to then go back and do the testing, or would they just get a historical pass?

DR. ASHAR: Yeah. My FDA colleagues are telling me yes, they would have to go back and accomplish that testing.

DR. HARRIS: Dr. Sood.

DR. SOOD: Thank you. Geeta Sood.

I think I've said this before, but I would want the therapeutic antibiotics to either be

Class II with clinical data required or Class III. But I agree with the others that I think the rest, including silver, etc., would be fine as Class II with the modifications.

Thank you.

DR. HARRIS: Dr. Hickerson.

DR. HICKERSON: From the standpoint of leaching, I'm not sure that if it leaches and it's not absorbed that that's a problem depending upon the amount of leaching that you have from that product. Your silver, if it does leach from your dressing for any reason, you've got to dump -- you know, somebody did something to the dressing itself, sterile water or anything else. You could put saline on it. It's probably going to tie up your silver and not be available to the wound bed, anyway. If it does leach, it's going to be tied up with the silver proteins that are in the wound bed and not be absorbed. So I don't know how that would be addressed in that case.

For some of the aspects with inhibited wound healing, I think most of these have probably gone through those tests in their 510(k). But the question there would come a little bit differently, too. If they're only used for a temporary dressing and it's for the wound environment, if it did show that it was somewhat of a delay in healing, would that be important in the overall role of that dressing for a short term, where then you may be applying something else to that wound? That's going forward. So those are some of the questions, I think, that make it even more difficult with what we're looking at.

DR. HARRIS: Well, I'd just like to comment quickly on a couple things that I know regarding silver. It actually is in the burn literature, a demonstration of burn dressings containing silver, and it has actually quantified exactly how much can be detected in the circulation following their use. So there is certainly a pharmacokinetic impact of silver dressings in burn wound patients. Whether or not that has clinical significance or not is another question.

The other issue about the ability to perform in vitro tests looking at the solubility of silver-containing products, that has been done and also seems to have fairly good predictive measures, whether it be by varying the type of solution in which you're incubating these devices and/or the conditions of an incubation. But you can derive some seemingly clinically relevant information from what would be an in vitro test. So I think there could be some reasonable information obtained through those sorts of special controls.

Dr. Miller.

DR. MILLER: I think that Class II is the most sensible classification because this is not life threatening, that there's not an enormous effect on human health except if you use an antibiotic, like Dr. Sood mentioned, and I think that shouldn't be considered the same. Or if the dressing is conceived as a drug delivery device, I think that's a totally different thing. If you're delivering lidocaine or if you're delivering steroids or anything with what you put on the dressing, that's a different type of consideration here.

And I think, also, there's no reasonable risk of injury from these things. I mean, they've been used for decades, and now we're starting from scratch on the use of these things, and we have no idea about what to expect from them, and they've been used for a long time, and there's not much of a record of people being harmed by them that we know of. So I think that Class II makes perfect sense.

DR. HARRIS: Dr. Alam.

DR. ALAM: I also think that Class II might allay some of FDA's concerns about particularly the risk of resistance that might be induced by some of these because if there were some antibiotics involved, presumably for those special cases where heightened risk was assessed, special controls could be implemented. That would be in addition to what's currently there, and that could, it sounds like, force manufacturers to then make sure they were in compliance with those special controls and provide a higher bar for those small

minority of products that might be there.

My understanding, also, for the sake of clarification -- we keep talking about antibiotics, and I keep getting confused a little bit. It is my understanding -- please correct me if I'm wrong -- that the class of dressings we are discussing might have antimicrobials, monograph based, ones used differently or admitted in this milieu, but they don't have any specific antibiotics known to be therapeutic antibiotics like gentamicin or anything else. They don't have an actual antibiotic in them; is that correct?

DR. SHERMAN: Rachel Sherman.

Two were bacitracin and polymyxin, not vancomycin and endomycin.

DR. ALAM: Thank you.

DR. SHERMAN: If I could ask for clarification from Dr. Miller. So if the claim were -- so now going to your drug delivery device point, if the claim were something like prevents itching or treats itching or reduces pain, would you consider that an indication with a drug delivery device?

DR. MILLER: Well, it depends on what the mechanism of reducing the itching is. If you're putting an ointment on and it has an antimicrobial in the ointment to keep the bacteria count down, but that's not the primary purpose of the ointment, then I think that's a reasonable claim. You're not delivering the antimicrobial to the wound; you're trying to deliver an anti-itch -- you know, maybe -- I don't know, an antihistamine or something. I don't know. But I think if it's intended to deliver the drug, and that's the primary mode of action of the device, then it doesn't fit in with what we've been talking about in this whole discussion, to me, because it opens up a whole other set of questions, but you have to demonstrate that what you're delivering is clinically relevant and important and all of that. I mean, I'm trying to discipline myself here to remember that we're just thinking about the dressing itself.

DR. HARRIS: But how are you addressing the issue of the unintended delivery of a drug?

DR. MILLER: Well, I think the question of leaching or things like that, I mean, you're correct, there could be an unintended delivery of the drug. That can be confirmed, I think, with in vitro studies and with even just laboratory studies. But I think you have to -- that's not the intent of the dressing, you know, to have the drug leaching in, to have the drug being delivered. If it's an incidental event, then you'd have to sort that out. That could be one of the criteria you'd look at.

DR. HARRIS: So I'm interested in asking the Panel, for those of you who have extensive experience or some experience treating wounds, when you see these wound dressings that are impregnated with various things, does that, in fact, influence your choice beyond -- I know you've mentioned earlier, Dr. Miller, that you use these dressings when there's odor that you want to address, but I'm curious as to whether there is a subliminal impact or influence on dressing choice when you see there are medications, because I do believe that many practitioners have a reflexive response to give drugs, to give antibiotics. You've got a wound, there's a problem, the patient's coming back every week, and I wonder whether we're not being -- there's some additional influence being exerted on our prescribing practices here.

DR. HUNT: I would say that I agree with you; that does happen. But in my experience, some of these dressings that I use are partly because you're able to reduce the number of dressing changes that the patient has to do. You know, I can remember when I first started in surgery where everything was like TID or QID dressing changes, and it's just problematic for everybody concerned, whereas now we have dressings that can be applied and maybe changed once a day or every other day, and it's just a whole different situation for the patient and the caregivers. And so to me, that's a huge advantage.

DR. ALAM: To answer your question, Dr. Harris, I don't think I personally -- and again, I don't treat burns. In full disclosure, I treat relatively modest, sometimes full thickness but always, almost always acute wounds, but I don't consider that a selection criterion as to whether there's something in it. In fact, I suspect I probably unsuspectingly occasionally use things with some medication in it. But the principal reason we often use things in dermatology is to create a barrier, maintain a moist environment, or sometimes protect the wound from injury or from reapplication of dressings. So those are the most common things, and those usually don't require a medication, and that's usually not a basis for selection.

I do think, going back to the issue that you're raising that, well, okay, maybe those of us in this room don't do this, but do a lot of other people do this? I think that's certainly possible, and I would suggest that FDA could certainly consider adding some labeling to the effect of making that explicit because we all, after many hours, have understood that we're talking about dressings and not about improving the wound, but we could add a disclaimer saying these dressings have not been substantiated to do certain things.

DR. HARRIS: Dr. Hickerson.

DR. HICKERSON: Dr. Harris, thank you, sir.

I agree with Dr. Alam, that in -- I do run a burn center, and I do run a wound care center that has a lot of large wounds and small wounds. The dressings that we're talking about, to me -- and what I try to relate to all of our residents is control moisture, just exactly what we're talking about. And if I'm concerned that I've got a bacterial load I need to take care of, then the silver nitrate, Sulfamylon, Silvadene, things of that nature that are true drugs that are going to approach that rather than the dressing itself.

DR. HARRIS: And so you think that the antimicrobial agents are there to help control moisture, or were put there by the manufacturer but are irrelevant to your prescribing

practice?

DR. HICKERSON: I don't think that they're irrelevant. I think they're there to control my barrier and anything that's there that's going to have a tendency to infect that wound from the outside rather than from the wound itself. A great example, burn wounds: When they first come in, they're going to be as clean as you're going to get them. And so from that standpoint, we're faced with a relatively clean wound once we wash everything up, get the dead tissue off, and then wrap them up. So we're really trying to prevent that infection coming in until we can get to the operating room and those that are going to need it.

We were talking about, earlier, that there are some wounds that probably don't need anything, that are so superficial. You're absolutely right. And in our vernacular in meetings, you'll hear people say, well, that's the type of wound that would heal with peanut butter. I've never seen a study that was done with peanut butter, but now we're seeing the honey. So now, at least, we're maybe a step closer.

(Laughter.)

DR. HARRIS: Ms. Lott.

MS. LOTT: So just to revisit one of my comments prior to lunch, what are the Panel's thoughts of lumping all of the solid wound dressings into kind of one category with the same controls, or do you guys feel it's appropriate to have subdivisions of that category? You know, back to the Band-Aid with Neosporin on it. Even if it does end up at Class II, should it be regulated by the same special controls guidance document that some of these more complex products are, or is there some delineation that we can further make for low risk, over the counter, minor cuts only?

DR. SHERMAN: Dr. Harris, could I just also ask you all to consider -- because burns keep coming up, and burns are a very different example than a decubitus ulcer. So it would also be helpful, as you're lumping and grouping, that you help us think about the different

large categories of wounds.

Thank you.

DR. HARRIS: Dr. Holmes.

DR. HOLMES: Jimmy Holmes.

On behalf of the burn community, we've offered before and we're offering again, we'll help you with the guidance document just for burns so you can get us out of that chronic wound thing.

With respect to further subdivisions, I actually like the one as it was presented yesterday, where if these were all to be classified as Class II devices, break them down by, if you will, their chemical constituents, with the metals, like silver and bismuth as one group, the guanides, the oxidizing agents, and the quaternary ammonium compounds. And I think one advantage of doing that also lends itself to better monitoring for resistance and especially from a special controls standpoint. I mean, if there's greater concern with chlorhexidine compared to silver, you may want to tailor some of the special controls from a resistance standpoint a little differently. So I mean, that's one thought along those lines.

DR. HARRIS: Just to follow up on that thought. So have you then determined which class you would feel it should stay in or what subcategory of compounds should stay in Class II as opposed to Class III?

DR. HOLMES: I'd make them all Class II.

(Off microphone comment.)

DR. HOLMES: All Class II with --

DR. HARRIS: You'd stick with special controls?

DR. HOLMES: Correct.

DR. HARRIS: Okay.

DR. HOLMES: All Class II with special controls tailored to their

antiseptic/antimicrobial subgroup.

DR. HARRIS: And recognizing that there are no special controls that we've heard about that will address antimicrobial resistance, your thoughts there?

DR. HOLMES: Monitoring alone would be a special control.

DR. HARRIS: Monitoring in what way?

DR. HOLMES: Emergence thereof.

DR. HARRIS: So that's postmarketing, it's already been approved?

DR. HOLMES: You could still put postmarketing requirements in place that would count as special controls.

DR. HARRIS: Correct. But I think, as FDA said earlier, that postmarketing is not thought to be a component of their safety and effectiveness evaluation. In other words, it's not as though you're kind of delaying that decision and waiting for the postmarketing information. It's an additional collection. I mean, that's my impression.

DR. HOLMES: Well, maybe it's time to rethink the way they think.

(Laughter.)

DR. HARRIS: Who was next? I think it was Dr. Sayeed.

DR. SAYEED: I just want to remind the Panel that, you know, the GAO report from last year, only 20% of devices are going through postmarketing surveillance to completion. So I know the FDA works very hard in what they do, but we have to be aware of that. So if we're requesting postmarketing surveillance, as Panel members, we have to understand that maybe that won't happen, and maybe doing the premarket studies would be a better way to start getting at some of this data versus relying on surveillance programs afterwards.

DR. HARRIS: Dr. Alam.

DR. ALAM: I wanted to address some of the issues that Ms. Lott brought up, specifically the idea of which ones of these might require special controls, and my thought

would be that the majority of these products probably wouldn't require additional controls beyond where they currently are, and they would stay in Category II as they're currently managed. The ones that we are sort of putting in a somewhat higher-risk bucket might require special controls, and that would probably include the ones that have some antimicrobials that we are worried about, in particular, things like the actual -- like polymyxin, bacitracin, and other antibiotics of those sort.

But I don't think -- I think we should be careful. If these things need special controls such as those cases, we should implement them. But it's a very disruptive thing, and it's creating a lot of work for FDA to just needlessly tack them onto every single product, so I'd say the majority of products probably wouldn't need them.

Now, with regard to other potential buckets, and I think other people have alluded to this already, but I would suspect one way to think about wounds that would be treated -- and there might already be some guidance about this -- would be body surface area in addition to acuity. So, for instance, small wounds or wounds smaller than a certain size, I suspect, would be much less concerning because whatever that potential risk, I suspect, might often be related to size of the wound. Now, that might not apply specifically to the microbial aspects of it. This may be a very small amount of the same. But I suspect a prolonged exposure over a larger surface area would often be more concerning, whatever risk there was. So I would suggest a small/large distinction in terms of wound size might be relevant.

DR. HARRIS: Dr. Burke, you had a question?

DR. BURKE: It's not a question, but again, everything that's Class II is still subject to the criteria of 510(k), which are very good criteria, in my mind, and I think that maybe in the labeling it could be required, is this allowed for children under 2 months, children under 2 years, whatever cutoffs the FDA usually has, and the size of the wound. I mean, I think that

they're two different things, and if we want a category for wounds and a category for burns and a category for catheters, I mean, that's fine because they're three very different kinds of indications.

DR. HARRIS: Dr. Campbell.

DR. CAMPBELL: Greg Campbell.

So at the risk of trying to simplify this -- and excuse me that I'm not a clinician, but it strikes me when I look at Section 513, it looks like, you know, unless there aren't special controls that we think could provide assurance of safety and effectiveness, we're then in a situation is the device life supporting or life sustaining, and I'm not sure that I've heard anyone be concerned about that. Is it for use that is of substantial importance in preventing impairment of human health? I'm not sure I heard that either, but maybe someone wants to weigh in on that. Or is the device -- or the device presents a potential unreasonable risk of illness or injury. And the reason that's important is if you're going to go to Class III, you're going to ask a company to do a clinical study and to answer that question, whether the device presents a potential unreasonable risk.

So what kind of study is going to be done for this wound healing product that's going to answer that? And so a question to ask is if we're interested in antimicrobial resistance, what kind of study would a company do that would try to address that risk? So that's my question.

And the other sort of parenthetical question is -- well, we talked about clinical data for catheter-related bloodstream infections, but it might be possible that you could use special controls for that. It's not clear. I mean, you might want a clinical study, but is it -- would one need to go to Class III in order to figure it out, or would the special controls be sufficient? So I'm not trying to answer the question. I'm just trying to pose it in such a way that I think it will be easier for the Committee to answer.

Thanks.

DR. HARRIS: So it's Dr. Hunt, then Dr. Miller.

DR. HUNT: So I appreciate the comments you made because what kind of study are you going to do to show that these wound dressings are not creating antimicrobial resistance in terms of the global issue? Because, again, remember that so many of these patients who have wound issues will be on oral or IV antibiotics in addition to whatever wound care they have. So that is going to be a really, really challenging endpoint to address.

The other thing is that with respect to the categorization of things, I do like trying to address whether it's an acute or a chronic wound because I think those are different issues. And then also the burns, I think, are sort of a different issue as well. And certainly the size of the wound has a major consideration for trying to address issues of systemic absorption and things like that, because a very small wound would have minimal absorption, whereas a very large wound, as described earlier, could potentially -- especially if you're applying this over a certain large surface area. So those all are things that should be included.

DR. HARRIS: Dr. Miller.

DR. MILLER: I agree with my colleague, Dr. Hunt, on breaking the wounds down. I think the wounds should be broken down by burn, chronic wounds, acute wounds, and catheter insertion sites. It makes sense to split those out. I think the agents should also be split out a little bit. I think these metals and the oxidizers and the antiseptics, I think Class II is perfectly adequate for them. If we're starting to talk about actual antibiotics that are targeted drugs, those we have to have a much more stringent attention to, and those may even be Class III. I don't know. I defer to your judgment on that.

The other thing I would suggest we break out is the purpose of adding the antimicrobial. If the purpose is to prolong shelf life, that's a totally different thing than

treating the wound. And so I think those should be split out, too. The concerns are vastly different, in my view, if you're adding an agent for those two different purposes. So it doesn't make sense to me to group those together either.

DR. HARRIS: We have Dr. Burke.

DR. BURKE: Just again coming back to the 510(k), that one of the tests is that you put the bacteria on a patch, and then you see if any colonies grow, and you test against two or three gram-positives, two gram-negatives, a yeast, and a mold. At least maybe you could do the tests longer. But if there were resistant organisms at the bottom of the patch on your agar, you get colonies of resistant bacteria. So I don't know how long you have to continue a test to say that resistant organisms didn't form. And, of course, you're not testing for every possible organism that could be in the biofilm of every wound. But I think we do have some indication of resistance, and the data presented by the presenters today, I mean, some of the things have multiple mechanisms, so there's less apt to be resistance, although I understand the importance of plasmid resistance. But I think we have a good indication, and as Dr. Hunt said, many of the patients are already on systemic antibiotics.

DR. HARRIS: Dr. Patel, then Dr. Reller.

DR. PATEL: Thanks. Jean Patel.

I'd like to just address this issue of drivers of resistance. So I would urge the Panel to think about preexisting resistance that occurs because of drivers outside of the antibiotics being used in the dressing. A good example is resistance to polymyxin B. Probably the biggest driver of plasmid-mediated resistance to polymyxin B is colistin used for food-producing animals outside of the United States. So those drugs aren't used for food-producing animals in the United States, but they are commonly used for raising food-producing animals in most parts of the world other than us. As a result, there has been an importation of bacteria with that type of resistance. So when you think about how that

could apply to the issues we're dealing with here, use of a product that has polymyxin B could select for that preexisting resistance on a plasmid. So we're not really worried about de novo selection of resistance, but selection of resistance that has been created by these other drivers.

I think that's important not only for exacerbating a resistance problem, so there are more resistant bugs because we're using more products with polymyxin B, but it's also a problem with the perceived efficacy of adding polymyxin B to the dressing. So I do think that these antibiotics are being added to these dressings because there's a perceived benefit in preventing infections, and I would say that that perceived benefit will deteriorate over time because of increasing rates of resistance.

DR. SHERMAN: Could I just ask to follow up on that? So however we define this or quantitate it, that is a very elegant description of a potential risk. So when we think about how these are used or thought of, one is to increase the shelf life. So I can think about how we could write a special control to measure whether the shelf life has truly increased, and then we could discuss risk and benefit, but I'm still struggling with the two that we discussed yesterday quite a bit: moist environment and decreased colony count on the dressing. It's still very unclear to me how we would measure those and how we would quantify the benefits of it, and we could balance it against the potential for risk.

DR. HARRIS: Dr. Reller.

DR. RELLER: To follow up on Drs. Hunt's and Campbell's comments earlier, this concept of risk, including societal risk and specifically antimicrobial resistance, is relatively new. I mean, it wasn't on the radar screen, you know, some years ago in consideration of drugs or drugs added to the compounds. And it's true that it's difficult, in the individual patient, to predict the effect on antimicrobial resistance. You know, I look at that question of balancing safety, avoidance of resistance, and the effect. I flip that thing around, and

that is we know that there is a problem with antimicrobial resistance, not necessarily in that individual patient but in a larger sense, as Dr. Patel mentioned. Consequently, in addressing this balance, I would emphasize the importance of demonstrating any efficacy.

When we reviewed in the Executive Summary the guidelines from the various societies that are involved in this area, I don't recall any of them, perhaps with the exception of silver sulfadiazine, and certainly not with polymyxin or with -- that any of them recommended, as part of the management, the care approach of having an antimicrobial agent. This includes diabetic foot ulcers, you know, etc. None of those guidelines. They either say the reviews are mixed or they proscribe, but none of them endorses this as a standard of practice.

And consequently, it's hard for me -- I think most of these things will stay in Category II. There may be some special controls that if they're not satisfied, they may be upgraded, and including in the list of things that I think deserve special attention are those things that are on our three lists. I think all of those should be looked at. You know, is there some noise, signal that they delay wound healing? Is it some signal that they sensitize? Is it some signal of toxicity? And then those things would be addressed.

You know, I'd save a lot of time, and I'd scrap white petroleum, mannitol, and sucrose. I just picked a random one out of each column on the list because those things, it's conceivable to me -- you know, just intuitively, they may be a combination, but they could probably be Category I. We've talked about upgrading. We haven't talked about downgrading if something is simple enough. And it seems to me, to parse out the broad sweep, the most inclusive category of Category II, to take it into, okay, we'll recommend downgrading some, possibly upgrading a few, and putting this group, either because of absorption or wound healing delay, on the watch list, so to speak -- I mean, giving special attention to those. And I appreciate Dr. Miller's comments about X, Y, and Z, and he

mentioned specifically delayed wound healing. In that case, it would seem to me you're sort of -- the product's neutral. Now, you've got a big lead weight around the product, namely, it delays would healing, which is intuitively not good. So the benefit of the added product in overcoming the wound, not the wound healing itself, but that the benefits of contained microbes or whatever the benefit is, is sufficiently high to offset a negative, and that's why I'd start out with animal studies, is which one of these things have negatives? And then it becomes special attention given to those things that have negatives, to even more important -- to show that there's some efficacy to it. Otherwise, you know, what are we achieving? You know, those are my thoughts.

DR. HARRIS: So a quick question to you. So what do you recommend doing with things that have no impact at all?

DR. RELLER: I mean, if the second ingredient in this compound, you know, they don't have any ups or downs to them, they're just there, I don't have any problem frankly with putting them in Category I.

DR. SHERMAN: Could I ask just a follow-up question? So if I follow you, because I thought you were going to say exactly the opposite --

(Laughter.)

DR. SHERMAN: So you have something and added something to it, and the something you add to it doesn't have a downside, but it doesn't have an upside. Why would you add it? I mean, to go back to the pink, making a dressing pink. That's terrific if you have a 2-year-old kid and pink is better. But what if not? In other words, if the second component you're adding -- and again, this is my drug background, where if you give one drug, if you're going to add a second one, you better have a really good reason to do it and know that -- why are you adding that second thing if it's not giving you something?

DR. RELLER: This is a sort of minimalist approach. I mean, my own personal -- I like

Tom Petty's comment in *Lung* some years ago, you know, about don't just do something, stand there.

(Laughter.)

DR. RELLER: Why have something in the product --

UNIDENTIFIED SPEAKER: It sounds least burdensome to me.

DR. RELLER: -- unless, you know, it's doing something that's beneficial? So I'd just as soon frankly have every added "drug" removed from the dressings unless they were shown to be beneficial, but you've got to balance that between the practical reality of the experience and so on. So, you know, sometimes if you -- you know, if you want to consider upgrading and taking a little, then you may give a little so that it looks like you're not being too rigid and you're open-minded about things.

DR. HARRIS: Well, before you break out in song -- Dr. Miller.

(Laughter.)

DR. MILLER: I think the answer to your question about how do you confirm that the dressing with the antimicrobial in it is effective, well, it seems to me you could just run a very simple study and just culture -- put inoculum on the dressing and see what you get after exposure to the dressing and with or without the antimicrobial. I can tell you from personal experience, if I have a wound that is very contaminated, and the dressing I take off is green, and I can't walk in the patient's room because it's an objectionable odor, and I give it like 2 or 3 days of using a dressing with one of these substances in there, and the dressing is white and there's no more odor, I mean, I don't have to do an exhaustive study to tell me that it's making a difference in terms of the colony count in the dressing. So it's --

DR. SHERMAN: I'm sorry, but can I just ask, do you think -- it sounds like you think you're having an impact on the wound.

DR. MILLER: I am always concerned I'm having an impact on the wound. If I put

something in the dressing that I can't be confident is 100% contained in the dressing, and it might be getting into the wound, it's going to impair wound healing. However, bacteria that are causing the problem are a far greater impairment to the wound healing than whatever I'm putting in the dressing.

And so it's a tradeoff you have to make between which do you want. I mean, I'd rather have the easier management for a little while and hopefully get the colony count down in the wound by repeated dressing changes and a nicer managed dressing protocol than -- you know, it's like two steps forward and one step back. I mean, if I'm taking two steps forward by adding the agent to the dressing, well, I may be taking one step back on the wound, but give me a few days to clean it up a little bit, and then we'll go back to a non-treated dressing. These are just judgments that you make which are hard to do a rigorous study on and confirm the right and the wrong on it.

DR. HARRIS: Dr. Sayeed.

DR. SAYEED: You know, one thing that I was thinking of when Dr. Reller was talking about downgrading some of these devices is if we're going to give credence to the placebo effect, and that's what we're going to be doing, is approving devices based on no effect and just on patient preference, I mean, I think that's the wrong thing to do. I mean, we're here to judge things based on safety and effectiveness. If you read the definition of Class II, I want to point this out again, that 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; by definition, you have to have evidence. I mean, that's the definition of Class II. And I would challenge Panel members to produce studies that provide assurance that these are safe and effective devices.

DR. HARRIS: Dr. Alam.

DR. ALAM: I had another point, but I just wanted to quickly comment on that point

you just made, Dr. Sayeed, and I hear what you're saying. I think patient-reported outcomes are increasingly recognized as a valid outcome, though. So I think if that is something that were present, I don't think that would be equivalent to a placebo effect. It's a valid outcome, and it might not be a traditional outcome in terms of effectiveness that we've looked at, but I don't think it can be entirely discounted.

I'd like to respond to an issue raised by Dr. Sherman about how we manage -- how we look at moisture in the wound. And I'm not sure exactly how we look at it, but it is very important. It's very, very important for healing of a whole class of acute skin wounds at various points. And I think there are some sort of commonsense ways of looking at it, which is probably some sort of model, in vitro or animal. I suspect it probably doesn't even really need to be an animal model, but certainly an animal model would suffice probably, to see how much moisture you got with a dressing of a certain type applied for a certain duration on a certain type of wound. But I think it is a sufficiently important and relevant feature of a dressing.

To go to Dr. Sayeed's point as well, what are these things actually doing? I think that is a good thing that dressings do, that does help the patient in terms of comfort. But at the very least, it avoids the desiccation of the wound, which, as we said before, is relevant. Now again, I understand we're looking at the wound dressing and not the wound, but I think it is an effect that is associated with the dressing without it interacting in any biochemical way with the skin surface.

A question I had for FDA was we have discussed the concern about antimicrobial specifically. I think several people have raised that. Can you give us a sense -- you probably don't have this precise number and maybe you do -- of how many of these combination products have polymyxin or bacitracin within them? Just in big terms, is it a few? Is it almost all of them? Do we have any sense at all?

DR. CHANG: I think there are less than five clearances with those compounds in them.

DR. HARRIS: I think it was you next, Dr. Hunt. Dr. Hunt.

DR. HUNT: So one other follow-up to your question, Dr. Sayeed, is in terms of the efficacy; I mean, what level of evidence is provided depends on, I think, the patient population you're studying and the agent that you're looking at. But I think, again, you're kind of lumping everything together, and I think there has to be some separation here, and as part of the 510(k), there is some evidence provided for the efficacy of the wound dressing. And so that needs to be -- and that's kind of some of the things we're looking at here with respect to efficacy and risk. But, you know, to use another rock-and-roll reference, you can't always get what you want, but you get what you need.

(Laughter.)

DR. HUNT: I mean, for some of these things, if they're so low risk and they are providing some benefit for the wound environment, then we need to look at that, and I don't think you can say, across the board, that for all wounds the moisture has to be a certain level for a certain period of time. We have to separate out whether it's an acute wound or a chronic wound, and we know that there are different requirements for these different types of wounds. So I don't think we can just lump them all together and say that they all require a certain type of clinical trial to demonstrate efficacy, because the endpoints will be quite different.

DR. HARRIS: Dr. Holmes.

DR. HOLMES: Jimmy Holmes.

Back to the definition of Class III or -- excuse me, Class II. As I read it here, you got the part about general controls by themselves are insufficient -- yada, yada, yada -- and there is sufficient information to establish special controls to provide such assurance.

Information and evidence are two different things. Words are incredibly important in all of this. And yesterday we talked about potential risks and mitigations of them and all of the options we had to mitigate those risks, and from what I can recall, the consensus, other than with potentially the delays in wound healing, as we discussed today, those risks could be mitigated with simple things that did not involve human clinical trials. Preclinical animal models are options.

I mean, in the very near future, we're going to be able to use artificial intelligence models to structure randomized clinical trials for physiological interventions. I mean, the possibilities that await us in the next decade are immense, but we came up with mitigating -- we came up with mitigations for the risks that don't involve clinical trials as the means for the special controls. So it's not evidence; it's information that a given method of analysis and study can be applied appropriately and answer the safety question.

DR. HARRIS: Dr. Ashar.

DR. ASHAR: Yes. I just have one clarifying comment and then one question. One is yes, as a special control, postmarket studies can be requested. Typically, the language in the special control indicates that the surveillance must be conducted and completed in accordance with FDA, as agreed upon, based on the postmarket surveillance protocol. So there would be some sort of, you know, question associated with that.

I just want to make sure that the Panel continues to think about different categories, and one category would be how we would bucket infected wounds versus non-infected wounds and perhaps healing wounds versus non-healing wounds.

DR. HARRIS: Okay. So what I'd like to do over the next 5 minutes before we take a break is go around the room and just get a very, very brief -- you've got 5 to 10 seconds just to say whether -- you know, maybe 15 to say what you feel in terms of the classification discussion; if you feel they should all be Class I, Class II, Class III, how you'd break them out,

if you want to subdivide, just so we get a general sense of how our Panel is feeling.

So I'll begin with Ms. Lott.

MS. LOTT: I feel that they should be largely Class II, regulated with a variety of special control documents. I do feel that solid wound dressings need to be further delineated by perhaps wound type, by minor, by size, as some of the other panelists mentioned, and maybe by over the counter. I don't necessarily feel that the same special controls and rigor are necessarily applicable to those different risk levels.

DR. HARRIS: Thank you.

Dr. Sayeed.

DR. SAYEED: I continue to believe, as I did earlier, that these devices should be Class III devices with the exception of the indwelling catheter. I understand what Dr. Holmes is saying in terms of sufficient information, but at the same time, we should be doing the right thing, and the right thing is to have nice, well, high-qualified or, I should say, robust studies to understand how our special controls are working. It basically says sufficient information to establish special controls.

DR. HARRIS: Okay.

DR. SAYEED: We don't have any of that information.

DR. HARRIS: Thank you.

Ms. De Luca.

DR. DE LUCA: Yes. I think I would go for Class III as well. Just from the overall feeling around the table, it seems to be going in that direction, and I certainly would like to give patients every leeway that they can get.

DR. HARRIS: Thank you.

Dr. Campbell.

DR. CAMPBELL: I guess I would probably say Class II for most of the kinds of

applications that one would see. I just have a hard time imagining what kind of clinical study you would do for -- which would be required for a Class III product to examine a particular risk and rule it out.

Thank you.

DR. HARRIS: Dr. Holmes.

DR. HOLMES: Overwhelmingly, I think all of the FRO products should be classified as Class II devices with the potential exception of the indwelling vascular catheter dressings, which I actually think should be downgraded to Class I.

DR. HARRIS: Thank you.

Dr. Elmore.

DR. ELMORE: Class II with special controls.

DR. HARRIS: Dr. Hickerson.

DR. HICKERSON: I, too, think Class II with special controls. And for moisture, you can even go bioimpedance. There are plenty of things that are out there that show that those controls can exist.

DR. HARRIS: Thank you.

Dr. Burke.

DR. BURKE: I think Class II with special controls, and the point is that we have -- that everything that will be admitted already is subject to criteria from 510(k), and given this discussion, we might add a few controls.

And secondly, as a clinician, I can't minimize what -- I cannot minimize the fact that having a patient not go through the pain and discomfort of having a bandage changed more frequently -- and as we said, seeing the green odorous material, if that is -- when that is eliminated and the bandage can be placed for a longer time, it's such a clinical advantage.

And third, if something meets criteria and is passed and we, as physicians, use it and

our nurses use it, if it's not working and it doesn't seem to be effective, we don't use it anymore. So I think that it's market driven.

DR. HARRIS: I'm going to cut you off there. Thank you.

Dr. Alam.

DR. ALAM: Class II with special controls. And I would suggest that, based on our discussions, we can stratify within the categories. So some might not need special controls, and some might need more stringent special controls.

DR. HARRIS: Dr. Hunt.

DR. HUNT: I would agree with what Dr. Alam said. And then the other issue is special controls. But I also agree that the central venous catheter dressings could be changed to a different class.

DR. HARRIS: Dr. Miller.

DR. MILLER: I think Class II for most of these things with the exception, perhaps, if you have a device with an antibiotic in it.

DR. HARRIS: Ms. Leach.

MS. LEACH: I would agree with Dr. Miller, Class II with the exception of those which have an antibiotic.

DR. HARRIS: Dr. Reller.

DR. RELLER: Class III, polymyxin --

DR. HARRIS: Turn your microphone on.

DR. RELLER: Excuse me. Class III, polymyxin and possibly bacitracin, with copper and other compounds that have been linked with plasmid cross-things, to put them on a watch list and review the literature and data and so on. The rest of them could be in Class II with the special controls. But I would have everything on the three sheets we got looked at with special attention to absorption, toxicity, sensitivity, as I mentioned earlier, wound healing.

DR. HARRIS: Great.

DR. RELLER: And that's it.

DR. HARRIS: Perfect.

Dr. Patel.

DR. PATEL: Class II with special controls for most of them. I agree with the exception for those with antibiotics.

DR. HARRIS: Dr. Sood.

DR. SOOD: I would do Class II (special controls) for almost all of them except antibiotics. And I would actually divide into three categories the antibiotics, the antiseptics, and some moderately more risky drugs and then the not risky. And the ones that are in the moderate, I would limit them to not over-the-counter use, if that's possible, so that it's under medical care.

DR. HARRIS: Great. Well, thank you all very much. We're going to take a 15-minute break. Panel members, please do not discuss the meeting topic during the break amongst yourselves or any other members of the audience. We'll resume at -- well, make it a 13-minute break. We'll resume at 3:30.

Thank you.

(Off the record at 3:17 p.m.)

(On the record at 3:30 p.m.)

DR. HARRIS: So I think it's time now for us to move to the second category of products, so Dr. Chang, if you'd please lead us through that reading of the question.

DR. CHANG: For Wound Dressings combined with Drugs formulated as a Cream, Gel, or Ointment, FDA has identified the following risks to health based upon review of the medical literature, information available to FDA on cleared products, and the Medical Device Report databases. Please comment on whether you agree with the Potential Risks

to Health presented below and identified in the overall risk assessment of these products within the product code FRO. In addition, please comment on whether any additional risks should be included in this overall risk assessment of a Wound Dressing combined with Drugs formulated as a Cream, Gel, or Ointment under the product code FRO.

Potential risks to health include:

- Adverse tissue reaction
- Delays in wound healing
- Incompatibilities with other therapies
- Increased risk of contributing to antimicrobial resistance
- Infection
- Microbial growth within a product
- Product degradation during shelf storage

DR. HARRIS: Okay, so I'll open the discussion now to the Panel. Do you have any comments regarding these potential risks for this particular classification of wound dressings?

Dr. Sayeed.

DR. SAYEED: I would just add to the list of potential risks to health, you know, that says product degradation, but I would say product transformation. If it's, you know, sitting on the shelf, it may degrade into a product that could be more toxic.

DR. HARRIS: Just for a point of clarification, is the meaning of product degradation due to potential microbial infection and thus degradation, and that's why we're now adding to this product an antimicrobial agent? Is that the logic behind that particular risk?

DR. CHANG: Product degradation during shelf storage could occur for devices as well as drugs or a combination of products for a variety of reasons due to storage.

(Off microphone comment.)

DR. HARRIS: For a cream, gel, or ointment, for it to degrade, and the rationale, then, for adding an antimicrobial agent, and this is one of the -- is the risk, then, being that the addition of the agent is causing it to degrade or behave differently over time? I'm just trying to get the correlation of the linkage between adding the microbial agent, antimicrobial agent to the gel, cream, or ointment.

DR. CHANG: That could be one reason that the product would degrade.

DR. SHERMAN: But we're also looking for your counsel because remember the rather lumpy list of claims we showed you yesterday, so that's a good question. Is it that it's added to prevent it, or does adding it, in fact, accelerate it? So we're asking you what you'd like to know to support that.

DR. HARRIS: Well, I'll just begin by saying that I can't, off the top of my head, think of any actual rational correlation between the two, but that could just be my own ignorance, but it would seem like we should at least have some sort of stability testing performed both with or without the additive to demonstrate that that additive is having an impact on the shelf life. Seems pretty straightforward.

Any other thoughts?

Dr. Holmes.

DR. HOLMES: Jimmy Holmes.

I'm going to trump your ignorance with my ignorance and --

(Laughter.)

DR. HARRIS: Which is very hard to do.

DR. HOLMES: I don't know, I may have you beat here when you hear this.

I'm just trying to wrap my brain around a wound dressing formulated as a cream, gel, or ointment. I mean, can you guys give me, as a clinician, some actual examples of that? I mean, can you mention product names, or you can call them by generic or whatever? I just

-- to me, there's no such thing.

DR. ASHAR: Okay, so -- and I think Dr. Chang can add anything I miss, but in general what we see with a lot of these products is that they're, you know, intended for, you know, creating a moist wound environment or for relieving itching or -- and more specifically for a variety of dermatoses, for radiation dermatoses and various other dermatoses. They often have a lot of botanicals included within them, so advice along the lines of how we should consider these additives would be helpful.

Going back to Dr. Harris's point, as we're discussing or as the Panel is discussing the risks to health, we're thinking about the product as a whole with all of the chemicals and the ointment together, but if there's specific risks that you think should be called out that's specific to the additive, you can certainly mention that, if you would like later mitigation measures to address those specific risks.

DR. MARQUART: So I can further clarify. So as a clinician, this was also confusing to me, but under FRO if there -- the name is Wound Dressing combined with Drugs, so it encompasses the wound dressings that you guys just discussed, the gels, creams, and ointments now, and the wound washes. So they're all under that category, and that's just the name.

DR. HOLMES: So is bacitracin ointment in this?

DR. MARQUART: So bacitracin ointment isn't. So what these are, as Dr. Ashar described, these are -- typically, they're the creams, gels, or ointments to treat dermatoses, radiation dermatitis, seborrheic dermatitis, with different ingredients that's under that, in that inclusive list of ingredients.

DR. SHERMAN: And if I could just add one thing, because I also had trouble with this. As I remember, these products can -- either they are on the market before '76 or they had to be demonstrated to be substantially equivalent to a product. So it's not as if FDA looked

at these and said this is just a terrific idea, and we're not saying it's a bad idea or a good idea. We didn't evaluate it and now -- again, my colleague from OCC will stop me if I say something wrong, if they are substantially equivalent to a predicate, they're legally marketed.

DR. CHANG: If I could clarify as well. The intended use for these gels, creams, and ointments have generally been to provide and support a moist wound environment, and by extension, that has included claims in some cases to relieve the symptoms of skin irritations such as dryness, itching, and pain and has also included indications for skin irritations and various dermatoses, as Dr. Marquart said.

DR. HARRIS: Dr. Alam.

DR. ALAM: Yeah, I think this category, I think it is confusing because these aren't dressings in the typical sense, but I think these are not generally things like bacitracin that have any active ingredients; they're basically barrier creams, that's really what they're doing. They're covering the wound in a way that's mitigating evaporation, and they're forming a physical barrier, albeit not with a rigid product, but with something that kind of sits there and covers the wound. And that process of creating that barrier, then, can improve the moisture within the wound, can keep the wound from -- the patient from sensing itch that they might without the barrier, but the main benefit is not to directly interact with the wound like bacitracin might, but really just to sit on top of it and stay there. And as for the ingredients that are added to it, I suspect those are done for a variety of reasons. Sometimes the additives are not for any exalted reason; it's just so that the cream doesn't look disgusting or smell bad or like run off the person's leg and not stay in place, so they're sort of fairly simple functional elements sometimes. Sometimes I suspect the additives have no known function, but they're probably just allowed because there's a 510(k) process in place that allows them to be there.

DR. HARRIS: So does anyone have any more comments regarding potential risk of this class of wound dressing other than those that are listed here, any that you'd want to add or perhaps subtract?

DR. CHANG: If I could just clarify a previous question. One of the questions was regarding product degradation during shelf storage, and I think part of your question was getting what the purpose of the antimicrobial agents would be in these products. In some cases, the antimicrobial agents are included to preserve the product if it's not sterile and also to prevent microbial growth if there are repeated openings of the package.

DR. HARRIS: Thank you.

Dr. Miller.

DR. MILLER: I think that with these ointments, with repeated applications you can build up layers of the material on top of each other where you put in a layer and then you get out 90% of it, you put another layer on, and you're building up these serial, you know, layers, and I think that is one potential risk of retained material on the wound with repeated applications sort of thing.

DR. HARRIS: So that would be one risk to be added --

DR. MILLER: Yes, correct.

DR. HARRIS: -- like we've seen before. Okay.

Dr. Holmes.

DR. HOLMES: I think, similar to the solid dressings, we need to consider systemic absorption as a risk, I mean especially with the botanicals and other --

DR. HARRIS: So I believe that's under the adverse tissue reaction before, and then we're going to talk about the controls, special controls next. I believe that's correct.

Any other comments about potential risk?

Dr. Sayeed.

DR. SAYEED: I just have a question on application. How are these gels applied? Are they right from the tube onto the wound, do you take your finger with a glove; how are they applied?

DR. MARQUART: So this is a diverse group. There are some that are over the counter that, you know, some have been cleared for over the counter use where a patient would be applying, you know, squeezing -- and it depends on how they apply it, if they squeeze it, you know, from the tube onto their hand or onto the rash or dermatitis they have, and then there's ones that are prescription that, again, would have instructions by the physician or the practitioner that sees them that they would apply it, you know, twice a day for a certain amount of time. So that when they're cleared for prescription use, we normally say like apply twice a day for up to 2 weeks or apply, you know, something like that.

DR. HARRIS: Dr. Sayeed.

DR. SAYEED: So do these products have instructions for use if they're OTC? I mean, a dollop or how -- the reason I ask that is because I think that just in terms of topical toxicity, you know, overuse by a patient of an OTC chemical, obviously that's problematic. And contamination obviously.

DR. ASHAR: So yes, our OTC products do have patient labeling.

DR. HARRIS: Okay. So let's move now to the controls, what sort of controls mitigating these risks, these potential risks.

DR. CHANG: For Wound Dressings combined with Drugs formulated as a Cream, Gel, or Ointment, the risk/mitigation table below outlines the identified risks to health and potential regulatory controls/data requirements that FDA could apply for each identified risk. Please discuss each of these potential controls and whether it, either alone or in combination with others, adequately mitigates the identified risk(s).

The potential mitigation measures are listed on the right and include:

- Biocompatibility evaluation
- *In vivo* evaluation
- Labeling
- Evaluation and identification of the risk and potential mechanisms for resistance development
- Labeling
- Sterilization validation
- Preservative effectiveness testing
- Shelf-life validation
- Labeling
- Antimicrobial effectiveness testing
- Shelf-life testing
- Labeling

DR. HARRIS: Comments.

Dr. Reller.

DR. RELLER: Barth Reller.

Dr. Chang, could you remind us, me, of what proportion of all the products in the PRO that are under consideration fall into the solid, lotion, and wash brackets? Containing drugs.

DR. CHANG: Yes. Within the FRO category of wound dressings containing, combined with drugs, I do not have specific percentages off of the top of my head. The majority are solid wound dressings; however, in recent years there have been an increasing number of clearances for gels, creams, and ointments and liquid wound washes, and that is why we're asking you to discuss each of these three categories.

DR. RELLER: Okay.

DR. HARRIS: I'm just curious, and maybe someone has this information. Are there alternative ways for preserving creams, gels, and ointments if the concern is preserving effectiveness or antimicrobial effectiveness testing, effectiveness other than adding an antimicrobial? In other words, other strategies that products use to extend their shelf life or to deal with repeat uses that differ from adding antimicrobial agent? I don't know if anyone has any information along that line.

DR. SHERMAN: Well, again, this is a little bit from the drug side, but -- and my CDER colleague is here. On the drug side we see antimicrobials added as a preservative, we see preservatives added as a preservative, and then the shelf life is measured. As for sterility, I think we all know adding antimicrobial can't preserve sterility; a product is sterile, and when it's opened, it is no longer sterile. So if your question -- I mean, perhaps what you're saying is would we -- these seem like answerable questions. In other words, if it claims to be a preservative and it's increasing the shelf life, we could ask that that be measured. If an antimicrobial is added so that you can open it more times and decrease the colony count, you wouldn't preserve sterility. If that's felt by the community to be something valuable, we could certainly ask for that.

DR. HARRIS: Well, I'm just struck by what I think was an impression I have regarding the solid wound dressings, that there's a bit of a Trojan horse here, that it seems more apparent that to add an antimicrobial agent to something that we're putting directly into the wound in the form of a cream, gel, or an ointment, and to suggest that we're doing that so that it will have a longer shelf life or it will prevent contamination of what's not on the patient just strikes me as an indirect way of actually applying an antimicrobial agent to the wound but not going through that regulatory process in order to do so.

MR. KITCHEL: Brandon Kitchel.

If I can just add to that, for solid wound dressings, the material composition allows them, most of the time, to be sterilized, and they are then single-use devices, so they're disposed of after use. For these types of products, due to the nature of the composition, a lot of times the same sterilization process isn't applicable to them. High heat or gas or -- you know, things can modify the gel in the liquid composition within these products and will compromise the constitution of that material, and as a result, some of these products are not provided sterile and therefore rely on these reagents in them for a preservative function.

DR. HARRIS: Is that true for gamma radiation of these products as well?

MR. KITCHEL: It's a good question. I believe gamma radiation could work for some but not all. I don't have a great answer for you about gamma radiation.

DR. HARRIS: Other than nuclear fusion or something, I don't understand how that would not be possible, but -- Dr. Hickerson.

DR. HICKERSON: But then I could foresee that if this was going to be a multi-use, that it wouldn't maintain the cleanliness of that product for the next use; once you broke that seal, then that would be gone.

DR. HARRIS: Well, I think in actuality, if you think about it -- I'm sure you have thought about it -- it's one thing to kind of reach into the container and take something out as opposed to squeeze something out without actually touching the -- you know, a no-touch technique, so one thing I was wondering, whether the risk-benefit is genuinely there.

Dr. Miller.

DR. MILLER: Yes, one anecdotal thing which is making me address this is, you know, patients will put -- have a closed wound, they'll put one of these topicals on there, and they'll keep applying it day after day, and then they'll come in with a skin fungal infection because it does such a good job of maintaining a moist wound environment that it is -- but

it's incompletely cleaned off that they will, right exactly beneath where the material is put, they'll have a *Candida* infection. So I think that, you know, the point of, you know, the residual material between applications needs to be made, and if not, the risk of, you know, side effects like cutaneous fungal infections is relevant.

DR. HARRIS: Dr. Alam.

DR. ALAM: I just want to respond to the comments about sterility and the microbial growth within the product and the inclusion of microbial agents as preservatives for multi-use tubes of creams or ointments. In dermatology, at least -- and again, I understand this is a subset of the overall number of wounds we're looking at -- we're often treating relatively small, relatively acute, sometimes chronic wounds, and also we're treating other dermatoses that may not be wounds in the conventional sense but entail some kind of dermatosis or some kind of skin rash, for lack of a better word. And in many of those cases, sterility per se is not something that, as clinicians, we need or require. And really, what we're looking for is reasonable cleanliness, and we're trying for these things not to be highly contaminated, but if somebody's putting an ointment on a patch of eczema, for instance, we know it's not sterile, they've already scratched that patch of eczema, but we're just trying to keep it moist so that the eczema might be mitigated. And so I don't think in general, for those indications, we're using this -- clinicians are not intending it as a drug delivery system, and while I don't know the concentrations of the preservatives, I would suspect they're not sufficient to do that, at least on small wounds or small sites. It's more just you don't want it to be grossly contaminated when you put this cream on.

DR. HARRIS: Ms. Lott.

MS. LOTT: Perhaps a special control that would be appropriate, back to what Dr. Miller mentioned, and possibly for a *Candida* infection would be, you know, a section required in the labeling for, you know, continued use can cause, you know, X, Y, and Z side

effects or -- I guess it wouldn't be a contraindication, but you know, something to make the user more aware of you're going to treat one problem but you may cause another one if you misuse it.

DR. HARRIS: I'd like to hear a little discussion about why they're there in the first place. In other words, we could come up with special controls to accommodate their presence, but do they need to be there at all if there are other techniques or strategies to either use the product in repeated fashion without contaminating it? You don't need a sterile product necessarily, and the shelf life issue is not really being addressed by the antimicrobial.

MS. LOTT: I guess I might have misunderstood what the point was. I thought it was from the user misusing the product and over-applying it and using it for too continued period of time. In that case, that's not related to the sterility or the shelf life. I was assuming it was a side effect of over-applying that particular medicine because you said it was due to the wound environment is now too moist and --

DR. HARRIS: Well, that may be --

MS. LOTT: -- you grew something else.

DR. HARRIS: That may be part of it. It could also be that you're killing the bacteria locally, and the fungus is now an overgrowth due to the application of topical antibacterial --

(Off microphone comment.)

DR. MILLER: I'm sorry. That's possible, but I think that the point I would make is that one of the possible risks is residual material left on the surrounding skin or the wound with repeat applications, and I think the mitigating measure would be simply labeling, just to inform the patient that, you know, if you use this more than once in a row, you've got to completely remove the previous product and reapply, you know, so you clean the skin

underneath. That was my point really.

DR. HARRIS: Dr. Sayeed.

DR. SAYEED: I just want to go back to the labeling issue. I think labeling, especially for gels, is very problematic. You know, we all have gels and creams at home, and I'd challenge anybody to say whether or not they use it as it's labeled; I mean, I certainly don't.

DR. HARRIS: Dr. Alam.

DR. ALAM: To Dr. Miller's point, I think that's a reasonable idea, and I think Ms. Lott raised that as well. I understand your comment, Dr. Sayeed. No one reads the labeling. Unfortunately, I think we're limited in our ability to influence people's use of this without -- not familiar with other methods that we can provide and some other educational methods, but however we convey this, whether labeling or some other educational method, I think having the patient cleanse the wound and including that as sort of part of their education, saying every X number of days the wound should be cleansed with something as simple as running water or soap and water, I think that would often be sufficient for these small wounds to remove any residual.

DR. HARRIS: So I'd like to hear someone tell me why they would advocate to have antimicrobials in these products at all.

DR. ALAM: Murad Alam.

I think the reason that antimicrobials at all, this is my understanding, at least in some cases would be if you have this tube you're opening and you're using over the course of 8 or 9 days, you don't want it around Day 4 or 5 to basically become a culture medium, so I think that would be one reason.

DR. HARRIS: And so I just wonder whether we could find other perhaps even physical mechanisms for preventing the contamination of the contents, for example, a filter at the tip. I mean, I'm just wondering, do we really think that this is the only solution? And

once again, I raise this question of is this just a Trojan horse mechanism for getting antibiotics into the wound and not having to go through the standard clearance process?

I'm not provoking any comments. Dr. Reller.

(Laughter.)

DR. RELLER: People know where I'm coming from, and that is I don't think antibiotics used for human therapeutic use should be in solid matrices, gels, lotions, ointments, and washes. Because if they're doing something, and you alluded to this, as an antibacterial or any anti-infective agent, then in effect, with the occlusive qualities, the other component becomes a drug delivery device and it's -- and I've not seen anything that suggests that having the antibiotic in the lotion is -- not that the antibiotics don't work, but in that milieu that it's effective. And then if it is effective, then it needs to meet the criteria for approving of a drug delivered in that method.

DR. HARRIS: Dr. Ashar.

DR. ASHAR: I think you're raising an interesting question, and that is, is what assurance do you have that other means of preserving a product have been exhausted before going to an antimicrobial to do this, to cause this effect. And you know, I was asking my colleagues if we are familiar with special controls along these lines to provide justification that other means have been exhausted, and off the top of our heads, we're not familiar with any such special controls. However, one could be potentially written if appropriate testing could be suggested along these lines for us to consider.

DR. HARRIS: Well, it just strikes me that part of this discussion is around the risk that we believe conceptually exists but have not been easily quantified or even identified, but one could argue that these are low-risk devices. But why incorporate any risk, even a conceptual one, if it is unnecessary? So that's the context for my comment.

Dr. Alam, then Dr. Miller.

DR. ALAM: I think that's a legitimate point, but I also think that we should be sure we're talking about the same thing. I don't think, in general, we're talking about antibiotics for humans here. I think these are generally what we consider preservatives, and similar things that might exist in food packages that might need to be reopened and used in -- I don't exactly -- but preservatives are fairly common. I don't exactly which ones -- I know, for instance, preservative containing saline has benzyl alcohol in it, but I doubt that if you gave someone an injection of preservatives containing saline, you would think that's going to provide some systemic benefit to improve their endocarditis or whatever. I think it's a different level of what it is. But to your point of, well, why do we even have that and how can we get rid of that, I'm not proposing this, but just as a hypothetical, one thing would be is to have single-use vials.

DR. HARRIS: Dr. Miller.

DR. MILLER: I have a couple of suggested possibilities of why it might be helpful to have an antibiotic added. If you have a patient who lives in the swamps of Louisiana with an open wound, if you have a patient who works in a waste treatment plant, sewage treatment plant cleaning out basins, or if you have a Kentucky horse farmer who is in horse stalls all day long with a high level of contamination all around him, perhaps a product like this with an added protection would make sense, you know, so it depends on the level of risk their environment poses.

DR. HARRIS: But those would be therapeutic indications.

DR. MILLER: No, it would be very -- you would be increasing the ability for the --

DR. HARRIS: The barrier function?

DR. MILLER: -- wound dressing to prevent contamination from a heavily contaminated environment. I mean, I'm just speculating.

DR. HARRIS: Sure. Yes?

DR. SHERMAN: Dr. Harris, I was going to echo your point. That's very close to reduction of risk claim, and for us, that would be a drug claim.

DR. HARRIS: So if there's no more discussion here, can we now turn to the classification slide? Thank you.

DR. CHANG: Consistent with Section 513 of the FD&C Act, please consider the following:

a. FDA believes that general controls, by themselves, are insufficient to provide a reasonable assurance of product safety and effectiveness. For Wound Dressings combined with Drugs formulated as a Cream, Gel, or Ointment, please comment on whether:
    i. sufficient information exists to establish special controls to adequately mitigate the risks to health and provide a reasonable assurance of device safety and effectiveness for this device type;
    ii. the device is life supporting or life sustaining, or for a use which is of substantial importance in preventing impairment of human health, or the device presents a potential unreasonable risk of illness or injury.
b. For the category of Wound Dressings combined with Drugs formulated as a Cream, Gel, or Ointment, please provide a recommendation regarding which products should be classified into Class II or into III. Please discuss the reasons for your recommendation.

DR. HARRIS: Discussion?

Ms. Leach, what do you think?

MS. LEACH: Fluryanne Leach.

I think they should be Class IIs. I keep hearing antibiotics rather than antimicrobials, and we shouldn't get the two mixed up. And I also think that if we -- I mean, I'm hearing

that some people don't think that we should even have these in creams and gels, but if we didn't, we'd have to go to single use, and that would be very expensive. We'd have to go to a product that had to be used very quickly once it was bought or acquired, and that, again, would be expensive. So I think there's a good reason for it, and it ought to be Category II with special considerations.

DR. HARRIS: Dr. Sayeed.

DR. SAYEED: This is interesting. I think I'm going to go with Class III for these products. There's even less information on these products than in our last discussion, so to me, you know, without adequate information and studies on efficacy and safety, we're just -- I'm not sure what we're approving.

DR. HARRIS: Dr. Holmes.

DR. HOLMES: Class II with special controls.

DR. HARRIS: Ms. Lott.

MS. LOTT: Class II, special controls.

DR. HARRIS: Dr. Campbell.

DR. CAMPBELL: So Class II with special controls. Let me just say something. If one worries about antimicrobial resistance, that doesn't, in my mind, mean that it has to be Class III. And the reason is you could do a clinical study within Class II that would say is there any added benefit associated with the antimicrobial, and so I think that's a possibility without going to Class III.

DR. HARRIS: Dr. Elmore.

DR. ELMORE: Class II with special controls, and I think this should be the same as the dressings where we would look at -- with the exception of antibiotics.

DR. HARRIS: Dr. Hickerson.

DR. HICKERSON: The first question would be are these preservatives they're putting

in, are these going back to some of the things similar to what we had in the solid dressings? Because I imagine that most of these are preservatives, preservatives such as the boric acids and things like that, some of the things that would be parabens and things along those lines rather than true antimicrobials. So from that standpoint, I'd say Class II.

DR. HARRIS: Dr. Burke.

DR. BURKE: Class II with special controls.

DR. HARRIS: We can just say -- Class II by definition means there are special controls, so we don't need to keep saying that part.

Dr. Alam.

DR. ALAM: Class II.

DR. HARRIS: Dr. Hunt.

DR. HUNT: Class II.

DR. HARRIS: Dr. Miller.

DR. MILLER: Class II.

DR. HARRIS: Dr. Reller.

DR. RELLER: The antibiotics in the strict sense, specifically polymyxin and possibly bacitracin, but especially polymyxin, Class III. And part of the consideration is there's a directive of least burdensome regulation. The difficulty or one of the problems of putting compounds, all of them, in Class III, I mean, that becomes -- assuming there's some utility to them -- to me, burdensome because of lack of availability. I mean, it's an overreach of the regulation. So I think this, again, is where one especially, possibly others, depending on, you know, review of the collateral damage related to antimicrobial resistance, there may be one or two or three more that come up, but certainly polymyxin. And the others I'm fine with at Class II, and some of them, you know, I don't have any problem downgrading them to Class I.

DR. HARRIS: Dr. Patel.

DR. PATEL: I think if the additive is a general preservative with no association with resistance, Class II. All others, Class III.

DR. HARRIS: Dr. Sood.

DR. SOOD: I'm having a little trouble wrapping my head around this category because I'm not quite understanding the additive piece, so looking through the list of all the additives, for some of the additives I would say even Class I, like glycerin perhaps or some of the other additives that are there. With the antibiotics, I agree with what others have said, that I'm not sure, like you had said, they're even needed. And then the others, I would say Class II.

DR. HARRIS: Ms. Lott.

MS. LOTT: I just want to clarify a point you made, and correct me if I'm wrong, but 510(k), in and of itself, is not a special control. Or Class II, in and of itself, is not a special control. A special control is an additional requirement like a guidance document or a recognized consensus standard that's added on as a requirement in addition to having to do a 510(k) for that product. And even all Class IIs don't necessarily require 510(k)s. So that -- in my understanding of the regulatory world, that wasn't entirely correct to say that we could just say Class II without saying special controls --

DR. HARRIS: So that --

MS. LOTT: -- as our recommendation.

DR. HARRIS: That may be my error, but --

DR. ASHAR: Okay, this might be semantics. As these are currently unclassified, the Panel is deliberating on how to classify them. If they choose to classify them into Class II, FDA will go back, and in carrying that out, we'd be drafting special controls based on this conversation, so as you're talking about categorizing it as Class II, we can assume that

special controls will be written based on the deliberations that you've had over the past couple of days.

MS. LOTT: But one of the questions, because it was a two-part question, and the first part was for us to acknowledge if there is enough information to create a special control and then to classify the device accordingly, so I'm just saying, the question didn't have both --

DR. SHERMAN: I think we were -- if we felt we couldn't develop special controls, that would bump them into Class III. That's what we're trying to say.

DR. HARRIS: Dr. Sayeed.

DR. SAYEED: I just have a question to the FDA. I know that we're deliberating, but -- Section (g)(1), I guess it's 21 C.F.R. 860.7(g)(1), what class does that relate to? Because the regulations states, the regulation for this states it's "the responsibility of each manufacturer and importer of a device to assure that adequate, valid scientific evidence exists, and to furnish such evidence to" FDA and "provide reasonable assurance that the device is safe and effective for its intended uses and conditions of use." That says evidence; it doesn't say information. It doesn't say -- it says evidence, which means science. So is that Class II or Class III?

UNIDENTIFIED SPEAKER: What page are you on in your handbook?

DR. SAYEED: Fifty-seven.

MS. KRUEGER: Angela Krueger.

So the regulation you are talking about is related to medical device classification procedures and the consideration of how we determine safety and effectiveness, and we've talked about multiple components of this regulation today in terms of what's a reasonable assurance of safety, what's a reasonable assurance of effectiveness, and what's valid scientific evidence. I think you have to look at those pieces collectively. I think you're

pulling out a specific portion of the regulation that doesn't necessarily apply to any one class. I think what it is telling you is how a manufacturer would provide information to the Agency to support valid scientific evidence, and as it's been considered in the context of information, sufficient information, I think we've outlined, and Dr. Ashar outlined earlier, what a valid scientific evidence may be, and that is a range of information. So I think that this is really getting at classification in this regulation. This part of the regulation is related to the responsibility of the manufacturer to provide valid scientific evidence.

DR. SHERMAN: And if I could add to that. So that was yes, we spent a lot of time yesterday because it's so complicated and there are so many products, but -- and correct me if I'm wrong -- I believe that you have specifically made the point several times you do not believe that valid scientific evidence or reasonable assurance and effectiveness, evidence of reasonable assurance of safety and effectiveness has been provided. But I believe -- you know, we're listening very carefully to everyone on the Panel, and I think there are clearly -- on the Panel who believe that there is reasonable assurance of safety and effectiveness for these pre-amendment devices, except we've heard a lot of concern from certain, from a number of people about the antibiotics, I'm using that specifically, not antimicrobials. So does that answer your question?

DR. SAYEED: I just wanted a clarification because in the guidance document that is on the slide, it says information and not evidence and so -- because that changes the discussion, in my opinion.

DR. HARRIS: I'd just like to ask a clarifying question as well. So since many of these products were approved through the 510(k) process and having done so through identification of substantial equivalence to a predicate device, is this actually an opportunity for FDA to re-review those products in a more broadly defined sense? In other words, are we actually -- can we ask questions, or can you ask questions about those

products now that were not required during the previous review process?

DR. SHERMAN: Right. Up until now, we've been able to determine whether they're substantially equivalent to something that was on the market, and it all ties back to pre-amendment. Based on the advice that we hear at this meeting, we will then go back, write a proposed rule seeking public comment on a proposed rule and a final rule in which we've classified them, and we, again, based on this and our research, can determine that additional information is necessary to be satisfied that there is reasonable evidence of safety and effectiveness.

DR. ASHAR: And that is for both the new products that would be coming under these regulations as well as the existing products already present in the marketplace.

DR. HARRIS: So I'm wondering, does the Panel feel that we can endorse the concept that the addition of antimicrobials, antiseptics, and/or antibiotics should have a definable and demonstrable benefit to endorse its inclusion? Is that a principle that we could support?

DR. MILLER: I think that ideally the end result of all these things should be a healed wound that's not infected, but getting there is a different problem than what we've been asked to address today. I think that we, you know --

DR. HARRIS: I'm not asking that question actually. I'm just saying if you're saying -- could you endorse the concept that a manufacturer would have to demonstrate that there's actually a justifiable rationale or reason that can be demonstrated to be beneficial for inclusion of an ingredient such as an antimicrobial, antibiotic, antiseptic in these products?

DR. MILLER: I think that they need to show a rationale for it, like the pigment. If you can show that there is a subset of patients, like 3-year-old, you know, young females who like pink, okay, then you can put that in the dressing, and there's a justifiable reason for it even if it has nothing to do with wound healing. So I think, you know, I don't think you

could just willy-nilly and without any justification at all add, put additives in your wound preparation, but I don't think that's what's happening here, and I don't think people are doing that. I think there's a rationale for each one of them of some kind and --

DR. SHERMAN: Rationale is one thing and evidence is another, so one might do a human factors study of 3-year-olds and see if they really do like pink better, to stick with our vantage.

DR. HARRIS: Dr. Sood.

DR. SOOD: I think we would all ideally love to see evidence in all aspects of this. For me, I would want to see evidence for sure for the antibiotics. The antiseptics, the silver, etc., I think that would be good, but I don't think a necessity, and that would partly depend on how you're defining evidence.

DR. HARRIS: Dr. Elmore.

DR. ELMORE: Yeah, just to clarify your question, is that if a manufacturer makes a specific claim about a product, should that manufacturer be required to validate that claim? Is that your question?

DR. HARRIS: I wasn't quite so general, but specifically around the addition -- so I think we would all agree that there are potential, if not conceptual, real risks associated with the widespread use of antiseptics, antibiotics, antimicrobials. So if someone is going to opt to include that in a product, that they then be able to demonstrate that it has a clear benefit so that whatever the risk that you're assuming is offset by something. In other words, if you can produce the same benefit without that addition, why would you ever assume that risk, no matter how small?

DR. ASHAR: If I could just -- we want our labeling to be truthful and accurate, so any claims should be justified, and it would be helpful to us if the Panel has recommendations about, you know, certain types of testing that would help justify some of these claims for us

to consider as possible special controls.

DR. HARRIS: Dr. Burke.

DR. BURKE: I think, again, we keep using the word antibiotic as opposed to antiseptic and antimicrobial, and I thought we were discussing antiseptics and antimicrobial, and so I don't know if we should go around the table and see how many people would say that an antibiotic should be a Class III and that everything most of us have said about Class II we thought we were talking about antimicrobials and antiseptics. But I don't know if that's necessary.

DR. HARRIS: By assumption that I didn't hear anyone who felt that an antimicrobial, I mean antibiotic should be a Class II, that they did feel these other types of antimicrobials broken down into the various classifications would all be under Class II with special controls.

DR. SHERMAN: Dr. Harris, so according to my notes, there were not only -- one, two, three, four Panel members specifically said antibiotics should -- or anything that -- Dr. Patel, you say it very nicely. Anything that can be linked to the plasmid and you get resistance should be Class III. The other Panel members, I believe, were silent on that.

DR. HARRIS: Why don't we have everyone speak up on that topic? So the specific question is do you feel that products containing an antibiotic should be Class III or Class II?

DR. ALAM: Would you like to clarify exactly what you mean by antibiotic, because I think that's -- specifically which products?

DR. SHERMAN: I think Dr. Patel and Dr. Reller said very nicely, so maybe I will let them say it, but can I just clarify one thing? When we talk about Class II with special controls and we talk about clinical studies, we're not talking about the kind of clinical studies that would help us define this problem, for what it's worth, anyway. Have you define the universe of -- Dr. Patel or Dr. Reller or whomever.

DR. RELLER: Barth Reller.

What I mean is an antibiotic that is used to treat human infection or prevent human infection, there are some of those, and those compounds that are not used therapeutically that are known or are become known to select for resistance in an indirect way because of co-carriage on a plasmid, for example, so that in effect, do the same thing as the antibiotic itself, though not specifically an antibiotic used for therapeutic purposes. So specifically, polymyxin and possibly some silver compounds, depending on availability, and copper, for example, chlorhexidine, I mean, those things that may be linked with antimicrobial resistance, they're sort of in the bullpen. The antibiotic used for human, out of the park, Class III. The others, under special scrutiny to assess what likely risk there is for encouraging, promoting, selecting antimicrobial resistance.

DR. HARRIS: Dr. Sood.

DR. SOOD: I have a question because this isn't really a classification that I've heard before in terms of the plasmid-mediated resistance in terms of defining an antibiotic per se, because in my mind I don't really put it in that category. I think of antibiotics as medications that are used for treatment or prevention of infection. Copper and those other types of resistance mechanisms, they may or may not be plasmid, they tend to be very low level. They may or may not be transmitted with other resistance mechanisms. I think, in my mind, and please tell me if I'm wrong, I think those are more hypothetical than like resistance to sulfur, sulfadiazine, or polymyxin, or bacitracin, which I would consider to be antibiotics.

DR. RELLER: We're in total agreement. I mean, I'm not trying to say that copper is an antibiotic in the strict sense; it's just that I think that we should not overlook the potential for promoting antimicrobial resistance in an indirect way with those compounds that are known to have that potential. They're not antibiotics, but they have an effect on

antimicrobial resistance that may be as important conceivably as the antibiotic itself used for human therapeutic purposes.

DR. HARRIS: So quick comment.

DR. BURKE: I think we should just specify that maybe most of us feel, or I feel, that anything that's a prescription topical antibiotic that the FDA has already defined as being prescription rather than OTC would be a Class III and that maybe we should pose that question. And I think that what you presented is very important because maybe the FDA should look back, now that we know about plasmid resistance, which we didn't know about years ago when Polysporin and neomycin were first on the market, that certain other things should be considered possibly someday, in a different venue to be reconsidered because of plasmid resistance. But I think for the purpose today, we could just say if we're going to ask, pose a question, we should just say should prescription topical antibiotics be considered Class III for this venue?

DR. HARRIS: I don't know if we have enough time to get a consensus on this topic. Anyone have comments about that specific question they'd like to make?

MS. LOTT: That topic is so big, it's so complex, and so multi-disciplinary and set at a healthcare level that I want to make sure we're not posing implications or regulations that are going to trickle down to manufacturers to find solutions to something that's a global problem, and it doesn't even have any recognized test methodology or ways to predict, and then all of a sudden we're going to make industry, particularly the 90% of companies who are 70% or less, be incumbent upon them to solve that problem.

DR. SHERMAN: But from one HHS point of view, it's exactly what we're asking farmers to do and other industries to do, so I think we need to take that off the table for a moment and concentrate on the public health implications.

DR. HOLMES: I have a question for the FDA. If we were to decide to make any of

these cream dressing, ointment things that have bacitracin or polymyxin in them Class III devices, what implications does that have for the over-the-counter market where both of those live every day right now?

DR. SHERMAN: So you're talking about -- do we still have our colleagues from OTC or -- no. What we're doing here is we're classifying medical devices, so the --

DR. HOLMES: I understand, an antibiotic's an antibiotic's an antibiotic, and it's --

DR. SHERMAN: Well --

DR. HOLMES: There will be unforeseen consequences of this decision, and you know, you've got stuff that's been out there in drug stores for decades.

DR. SHERMAN: If we were to classify, if FDA were to classify these wound dressings that contain, let's say, bacitracin as Class III, that does not impact a drug that has either been -- is under monograph or has been approved under an NDA as an OTC. So we're not going to go to Walgreens and rip them off the shelves, if that's your question.

DR. HOLMES: No, I'm not worried about it because I don't use the stuff, but -- you know. It's just it's a curiosity because these decisions, the results of these -- the decisions may be made in a vacuum, but the results of the decisions never repercuss in a vacuum.

DR. SHERMAN: Right. We're well aware of that. It is important, you know, to getting back to evidence, that if it's under a monograph, the monograph system has its bombs, but -- or if it's under an NDA, it isn't at the evidentiary standard for those.

DR. ASHAR: I'd like to add, I think what we're trying to do is make sure that this is a scientifically grounded discussion, and you're absolutely right; the conversation that we're having today could have implications to other things. That's something we will need to reconcile, and we'll need to be even-handed about doing that, but the charge of this Panel, I think, is enormous enough, and that is taking a look at these 700 products and helping us rationally classify them.

DR. HARRIS: Dr. Murad. I mean, Dr. Alam.

DR. ALAM: I just want to make it clear because I think we were having a little wrinkle as to what we all meant when we went around during the first time, so I want to make it explicitly clear that what I meant is, in fact, what I said, that I would like all of these to be classified in the II category and none of them to be in the III category. So I think maybe some other people might feel differently, but I just wanted to clarify my own views.

DR. HARRIS: Okay. So in the interest of time, may we please move to the third category?

DR. CHANG: Liquid Wound Washes combined with Drugs: For Liquid Wound Washes combined with Drugs, FDA has identified the following risks to health based upon review of the medical literature, information available to FDA on cleared products, and the Medical Device Report databases. Please comment on whether you agree with the Potential Risks to Health presented below and identified in the overall risk assessment of these products within the product code FRO. In addition, please comment on whether any additional risks should be included in this overall risk assessment of Liquid Wound Washes combined with Drugs under the product code FRO. Potential risks to health include:

- Adverse tissue reaction
- Delays in wound healing
- Inability to remove wound debris and foreign materials
- Incompatibilities with other therapies
- Increased risk of contributing to antimicrobial resistance
- Infection
- Microbial growth within product
- Product degradation during shelf storage

DR. HARRIS: So does anyone have any issues regarding these potential risks, any

risks they'd like to add or remove?

Dr. Elmore.

DR. ELMORE: Just one question: Does it make sense to include inability to remove wound debris and foreign materials in this category? The wound washes, it seems to me, wouldn't be adding to that problem. If they were there already, you're washing it. I'm just trying for some clarification here.

DR. HARRIS: I guess in the broadest sense, the inability to remove wound debris and foreign material would render the wash ineffective. I don't know if that's necessarily a risk, but if it's not able to do that, then it's not really serving its primary function.

Okay, then can we move to the actual special conditions? Controls.

DR. CHANG: For Liquid Wound Washes combined with Drugs, the risk/mitigation table below outlines the identified risks to health and potential regulatory controls/data requirements that FDA could apply for each identified risk. Please discuss each of these potential controls and whether it, either alone or in combination with others, adequately mitigates the identified risk(s). The only new one, I believe, is labeling for inability to remove wound debris and foreign materials and bench performance testing.

DR. HARRIS: Discussion?

Dr. Miller.

DR. MILLER: Mike Miller.

I guess I would just alter a little bit that fourth one there, inability to remove and change -- I mean, change it to something like, I don't know, inadequate removal or -- I think the thing we're trying to alert people to is that, you know, if you need surgical debridement, your getting the wound may not be adequate for you, so I mean, I think that some language pointing out that a wound wash may not adequately remove the debris is better language than just inability to remove it; I mean, does that make sense?

DR. HARRIS: Ms. De Luca.

MS. DE LUCA: "Difficulty in" instead of inability.

DR. MILLER: Yeah, or incomplete. Possibly "possible incomplete removal of" or something like that.

DR. HARRIS: Dr. Hickerson.

DR. HICKERSON: But then on the other hand, you may be needing to wash that more than once to remove that, so then do you have to set a time frame, do you have to set numbers down? Because nothing's going to remove debris like your surgery will, so therefore we can't expect these to get that precise.

DR. ASHAR: If I can offer some clarification. When we look at the identified risk, those are identified risks to health, so hopefully -- I mean, they are risks. You know, you could also consider risk of an ineffective product, but we're looking at identified risks with respect to risk to health.

DR. HARRIS: So Dr. Burke.

DR. BURKE: I just have one comment. Should these washes be rinsed afterwards with normal saline? Because there are a mixture of chemicals, and very often, we rinse something and then rinse it after with saline, so I don't know if that's specified in the products. Or this is the wash, and the residue of the wash remains on the wound.

DR. CHANG: I am not sure if I can speak for all of the instructions for use, but I believe in general that they do not state that you need to rinse afterwards with something else.

DR. HARRIS: So I have to say that my opinion in this area is overwhelmingly influenced by my training experience as a general surgeon. General surgeons have battled with the issue of the value of irrigation and the composition of the irrigant for seemingly eternities, and what we seem to have learned is that adding anything to the irrigant has

virtually no advantage. The only advantage is the volume with which you irrigate. So I find, in this class, even less of a compelling reason for the addition of antimicrobials unless, once again, we're talking about shelf life or preventing residual contamination of that material. But any agent that would have an antimicrobial function is, I think, going to be irrelevant in terms of its efficacy in treating that wound.

Dr. Alam.

DR. ALAM: I think that sounds very reasonable, Dr. Harris. I guess one question I would have, and I think maybe you've answered it, is that is the primary indication for this class of wound washes, irrigation? Because if it is irrigation, then I would tend to agree. I'm not really sure why there's lots of stuff in it if it's just a physical process of removing debris from the wound site. If there are other indications for these products, then I would suspect there's probably some rationale to having other active ingredients or agents within. But barring that, the only thing that I'd want to do is make sure there's something in it, minimal something, to keep it from being contaminated.

DR. HARRIS: It also raises the question if you're actually influencing the wound, why is it necessarily even in this classification at all? Because we've been talking about things that contain these products to really protect the product, not to treat the patient. This seems to me to be a direct therapeutic.

DR. SHERMAN: Then you would be advising us to put it in Class III and have data to support that claim. It's treatment, because it's a treatment claim.

DR. HARRIS: Dr. Hunt.

DR. HUNT: But it seems to me it would be similar somewhat to the gels in that having preservatives to prevent contamination from repeated use so that a patient can take this home and use it for several times without having to have single use, as was brought up before, so to me that would be an important component. And then also, depending on the

type of wound, if there were something to break up the debris within the wound wash, that seems like that might be an indication as well.

DR. HARRIS: But isn't that a therapeutic, the second?

DR. HUNT: Well, maybe to break up debris, that is not necessarily a therapeutic in terms of treating infection or something like that.

DR. HARRIS: Well, it's a form of debridement, which we would all agree is a fundamental tenet for, you know, treating necrotic wounds.

DR. HUNT: But so is just putting a dressing on and pulling off the dressing, and that it debrides the wound, you know, so I think doing a wound wash or using a gauze dressing and using that to debride the wound when you take it off, I mean, that's a therapeutic intent, too, that you might just use with regular gauze.

DR. HARRIS: Dr. Chang.

DR. CHANG: Cynthia Chang.

If I could clarify two items: One is regarding the purpose of adding additives into liquid wound washes. In some cases, products have antimicrobials to minimize growth during shelf storage or after repeated opening of a container that's for multiple use; in some cases, products have been sterilized and still have antimicrobials in them; in some cases, products do not contain antimicrobials but are sterilized and labeled for single use. So there is a wide range of reasons and intended uses related to these products and their components. Regarding the inclusion of liquid wound washes combined with drugs in this FRO category, part of it may be related to historical reasons. One is that the liquid wound washes are intended to primarily physically remove materials from the wound, and as that is considered a device and physical mode of action, that has been historically part of the reason they've been included in this.

DR. HARRIS: Ms. Lott.

MS. LOTT: Given that the FRO code is specifically for wound devices containing drugs, what is sterile water for irrigation that doesn't contain a drug or antimicrobial, what classification is that? Does it have a separate product code or --

DR. CHANG: In some cases, there have been clearances for liquid wound washes that are either sterile saline or sterile water that are not combined with drugs; however, those are not the purpose of this discussion.

MS. LOTT: Yeah, I guess I'm just curious because if those are not classified as medical devices, then why does adding a drug to it make it a medical device?

DR. SHERMAN: Others can correct me, but I think it's the intended use, to serve as a wound wash.

MS. LOTT: If sterile water for irrigation without a drug is used for a wound wash, it is a device, but it doesn't fall inside of FRO; is that correct?

DR. SHERMAN: FRO is combinations. We're looking -- this meeting is an attempt to classify the combinations, so we're only focused on combinations.

MS. LOTT: Surgical debridement is not --

DR. ASHAR: I understand -- this is Binita Ashar.

I understand it's challenging. If you pick out any one product, you start looking at the idiosyncrasies of it and the history of it, and I think, you know, what we'd like for this Advisory Committee to do is kind of -- as I've said before, look at categories and give us general principles and guidelines to go on. We're seeking to regulate the majority, recognizing that there may be outliers and may be ramifications, and those we're going to have to reconcile as we attempt to move forward.

DR. ALAM: I would suspect a fair number of items in this category would seem to me to be Category I even, assuming they didn't have these antimicrobials and the ingredient they had was something relatively benign, which may be not of tremendous use, but if it's a

really benign ingredient and you're basically just using essentially a dilute solution of water, that would worry me much less because there's nothing in contact with the patient's skin for any length of time, and after all, even just water has all kinds of -- I mean, it is -- it's not really -- it is a combination product. There is trace amounts of all kinds of stuff in it. So I think you'd have to put that bar in a reasonable point, but I think some of these things would be probably no more different than running a scalpel blade over somebody.

UNIDENTIFIED SPEAKER: Dr. Alam, could you give us any examples of what would fall in that category?

DR. ALAM: You know, I really can't because I can say this is an area of expertise more for the surgeons because we don't use a lot of liquid wound washes in routine dermatoses. I mean, there probably are some things that would fall in this category, but it's -- we're not usually debriding things, and it sounds like these are often used for debridement, so I defer to my colleagues.

DR. HARRIS: Dr. Holmes.

DR. HOLMES: Dr. Alam, I agree with you. And the things that immediately come to my mind are sodium hypochlorite and hypochlorous acid. I mean, you know, let's face it, it's bleach with water. I use it to clean the bathroom. Why is it a regulated device? Just because somebody mixes it up and puts it in a pretty little bottle. I mean, at most, those two should be Class I.

DR. HARRIS: Dr. Miller.

DR. MILLER: An example which comes to mind for me is if you're going to use an oral irrigation, they taste terrible, so you add like a mouthwash-type thing or something so it tastes better, has no therapeutic effect on the wound, but it just makes it more pleasant to use. So that's when you have an -- when you have this type of thing, this is what I'm thinking of when I'm thinking of this category. I agree with what was said earlier, that

probably most of these could be Class I. They're in contact so briefly and the risk is so minimal, if anything, that I'm not sure they even justify Class II, the vast majority of anything in this grouping.

DR. HARRIS: Dr. Sood.

DR. SOOD: I actually just have a clarifying question because I'm trying to understand this class a little bit better. Does hypochlorous acid, we use that in the burn unit, is that one of the products, things like Hibiclens, are those the kinds of things that we're talking about here?

DR. CHANG: There are liquid wound washes that include antimicrobial agents such as hypochlorous acid; however, there may be some nuances in terms of what is considered a drug and what is considered a combination product regulated as a device, and that's not really something that we would want to go into detail about here, but really focusing on the risks of combination products that are liquid wound washes.

DR. HARRIS: I would just say that -- and there are obviously people here who have much more experience running wound clinics than I do, but I recall, as a trainee, that we used to use dilute chlorine bleach, so-called Dakin's solution, for our wounds, and we were subsequently instructed years later that that was actually deleterious. So I think that this idea that because some things are kind of available even in the grocery store or on eBay, that they should be safe and regulated and they're very low risk fashioned by the FDA may not be reflective of best evidence or an evidence-based practice.

DR. HOLMES: I got the same party line about Dakin's when I was a resident, and it actually turns out to be incorrect. I mean, it's not that -- it's not as deleterious as we were led to believe. I mean frankly there are better options out there, at least here in the developed world, but it's not the devil that we were taught in residency.

DR. HARRIS: So if we can -- oh, Dr. Sayeed.

DR. SAYEED: Just a question for the FDA. How big are the bottles, and if you consider toxicology when you open these bottles and are exposed to any type of the evaporated liquid? There's concerns for pulmonary fibrosis and pulmonary edema secondary to these exposures.

DR. CHANG: The bottles may vary in size. Some are single use, and some may be labeled for multiple use. I'm sorry I can't be more specific than that. Toxicology is considered in -- as part of biocompatibility evaluation where we look at the materials and the toxicological risk profile of the materials that are included and can be evaluated through biocompatibility testing.

DR. HARRIS: Okay. So I'd like to just quickly go around the room and get, once again, everyone's comments regarding classification of liquid wound washes combined with drugs.

Ms. Lott.

MS. LOTT: Class I.

DR. HARRIS: Dr. Sayeed.

DR. SAYEED: Class III.

DR. HARRIS: Ms. De Luca.

MS. DE LUCA: Class II.

DR. HARRIS: Dr. Campbell.

DR. CAMPBELL: I say Class II, and I just want to say that within Class II, you can do clinical studies if you're concerned about an antibacterial agent for any of these types of devices that we've talked about here today.

Thanks.

DR. HARRIS: Dr. Holmes.

DR. HOLMES: Class I for the majority of them. I would imagine there's some that

would fit into Class II. And any that utilize a true antibiotic, Class III.

DR. HARRIS: Dr. Elmore.

DR. ELMORE: Class II.

DR. HARRIS: Dr. Hickerson.

DR. HICKERSON: Class II for the majority of these. Some, I think, could be Class I. Those with antibiotics, Class III.

DR. HARRIS: Dr. Burke.

DR. BURKE: Class II.

DR. HARRIS: Dr. Alam.

DR. ALAM: I think most -- sorry. I think most would be Class II. I think some might be Class I. I think the only restriction against making more Class I would be what if people don't wash the stuff off, which I think is certainly a possibility.

DR. HARRIS: Dr. Hunt.

DR. HUNT: Class II. And then I also just have one question. So some of these things that we find in these wound washes you could also buy over the counter, it's like household cleaning products, so I just wonder how that's regulated because if someone sees that the same ingredients are in those, then how is that regulated?

DR. SHERMAN: FDC would regulate any household item. If you were to decide to, for example, then -- Clorox and try to study it for warts, you would submit an NDA to CDER or -- so in others words, if it's available in the grocery store, it's available in the grocery store.

DR. HARRIS: Dr. Miller.

DR. MILLER: I think Class I for most of them. I think for ones with real antibiotics in them, Class III.

DR. HARRIS: Ms. Leach.

MS. LEACH: I agree. I think most of them can be Class I. I'm thinking of the large bottles of normal saline that we use for irrigation that have preservatives in them, that can be Class I. And there's others like that, also. There's a few that, with antibiotics, that should be Class III.

DR. HARRIS: Dr. Reller.

DR. RELLER: Barth Reller.

I'm in agreement with Drs. Holmes, Hickerson, and Leach, that if a product, for example, has hypochlorous, is not shown to be -- and there's evidence that it doesn't delay wound healing, which would be in the Class II category, by animal studies, you know, and then -- and some of them would be down-classified. Many of them would remain in II, and the antibiotics in the strict sense, III. As they've stated.

DR. HARRIS: Dr. Patel.

DR. PATEL: I agree with what Barth just said.

DR. HARRIS: Okay.

Dr. Sood.

DR. SOOD: I think I'm in agreement with what everybody says, depending on the additive agent, either Class I, Class II, and antibiotics, Class III.

DR. HARRIS: Okay.

Yes, Dr. Elmore.

DR. ELMORE: Dr. Elmore.

In the presentation, it indicated that for liquid wound washes there were no antibiotics, and is that -- I mean, that's what I see in the presentation under antimicrobial. So that wasn't a consideration for me because I didn't see it in that list in the presentation from today.

DR. HARRIS: Okay, does anyone have a final burning comment?

Dr. Reller.

DR. RELLER: I appreciate the comment just made, but I think one of the things that the FDA is looking for from this committee is not only what to do about existing things, but what the bar should be for things that might come down the road.

DR. HARRIS: Ms. Lott.

MS. LOTT: I just want to thank the Panel for all the creative solutions that they proposed today. I think the FDA really has a lot of places to move with how these products should be appropriately regulated, especially using the least burdensome approach. You guys came up with some creative endpoints, some reasonable classifications, and I really hope it helps the FDA move forward in a way that provides both safety and efficacy in a least burdensome fashion for manufacturers to be able to implement.

DR. HARRIS: So I'd like to thank the Panel, the FDA, and Dr. Gottrup for their contributions to today's classification panel meeting.

Dr. Ashar, do you have any final comments?

DR. ASHAR: Yes. I would also like to thank the Panel. I think what we did is we gave you approximately 100 pages to review; we then asked you to travel and in some cases have flight delays, and then put you through 2 days of grueling discussion, so we sincerely appreciate your commitment and hope that we haven't tortured you too much so you will come back again. Thank you.

DR. HARRIS: I now pronounce the -- Dr. Sayeed, did you have a final comment?

DR. SAYEED: No.

DR. HARRIS: No. I now pronounce the September 21st, 2016 meeting of the General and Plastic Surgery Devices Panel adjourned.

(Whereupon, at 4:55 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

GENERAL AND PLASTIC SURGERY DEVICES PANEL

September 21, 2016

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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