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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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NEUROLOGICAL DEVICES PANEL

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June 3, 2021
9:00 a.m.

Via ZOOM Videoconference

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OPEN PUBLIC HEARING SPEAKERS:

DIANA ZUCKERMAN, Ph.D.
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M E E T I N G

(9:01 a.m.)

DR. JENSEN: I would like to call to order the FDA's Center for Devices and Radiological Health Neurological Devices Panel of the Medical Devices Advisory Committee on June 3rd, 2021. It is now 9:00 a.m.

I'm Dr. Mary Jensen, the Chair of this Panel. I'm an interventional neuroradiologist and a Professor of Radiology at the University of Virginia.

I note for the record that the members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel participating in the meeting today have received training in FDA device law and regulations.

For today's agenda, during Session I, the Committee will discuss and make recommendations regarding the classification of vapocoolant devices, which are currently unclassified preamendment devices, to Class II (general and special controls).

During Session II, the Committee will discuss and make recommendations regarding the classification of acupressure devices, which are currently unclassified preamendment devices, to Class I (general controls).

During Session III, the Committee will discuss and make recommendations regarding the classification of electro-acupuncture stimulators, which are currently unclassified preamendment devices, to Class II (general and special controls).

FDA is convening this meeting to seek expert opinion on the classification of these devices.

I want to lay down a few ground rules in this virtual environment. If a panelist wants to ask a question, please use the hand-raising function on your Zoom platform and I will get to your questions as we proceed throughout the day. We want to prevent multiple persons from speaking over each other as we proceed, as this entire meeting is being transcribed for

the official record.

Before we begin, I would like to ask our distinguished Panel members and FDA staff attending virtually to introduce themselves. When I call your name, please state your area of expertise, your position, and affiliation.

Dr. Patrick Lyden.

DR. LYDEN: I'm Pat Lyden, I'm a neurologist at USC in Los Angles. I've run large clinical trials in stroke and I have a basic science lab in stroke, as well.

DR. JENSEN: Thank you.

Dr. Julie Pilitsis.

DR. PILITSIS: Thank you. My name is Julie Pilitsis, I'm a neurosurgeon and a neuroscientist in Albany, New York. I run the basic science department in neuroscience, and my research interests are on next generation devices and outcomes.

DR. JENSEN: Thank you.

Dr. Stavropoula Tjoumakaris.

(No response.)

DR. JENSEN: Okay, so we're going to move on to the next panelist, Dr. Karen Johnston.

DR. JOHNSTON: Hi, good morning. I'm Dr. Karen Johnston, I'm a vascular neurologist and Professor of Neurology at the University of Virginia.

DR. JENSEN: Thank you.

Dr. Earl Ray Dorsey.

DR. DORSEY: Good morning, Dr. Jensen and fellow panelists. My name is Ray Dorsey, I'm a neurologist at the University of Rochester where I direct the Center for Health and Technology.

DR. DORSEY: Thank you very much.

Mr. Elijah Wreh.

MR. WREH: Thank you, Dr. Jensen.

Hi, everyone. My name is Elijah Wreh and my expertise is regulatory affairs, I work for Zimmer Biomet, and I'm the Industry Representative. Thank you.

DR. JENSEN: Thank you.

Dr. Sujay Galen.

DR. GALEN: Good morning, Dr. Jensen and fellow panelists. I currently serve as the chair to the department of physical therapy here at Georgia State University in Atlanta, Georgia. My expertise is in wearable technology. I'm also a biomedical engineer by training. Thank you.

DR. JENSEN: Thank you.

Dr. Stephen McDavitt.

DR. McDAVITT: Hi, good morning. I'm Stephen McDavitt, I'm a full-time assistant professor at South College in Knoxville, Tennessee, a hybrid education program. I'm a practicing physical therapist for about 45 years, and thanks for being on the Panel.

DR. JENSEN: Thank you.

Dr. Rory Cooper.

DR. COOPER: Good morning, everyone. I'm Dr. Rory Cooper and I'm a bioengineer by training, specializing on assistive and medical devices. And I'm a professor at the University of Pittsburgh and a senior career scientist at the U.S. Department of Veterans Affairs.

DR. JENSEN: Thank you very much.

Dr. David Kennedy.

DR. KENNEDY: Good morning, everyone, honored to be here. I'm D.J. Kennedy, I'm a professor and chair of PM and R at Vanderbilt University Medical Center. My research

expertise is focused on interventional spine.

DR. JENSEN: Thank you.

Dr. Karen Anderson.

(No response.)

DR. JENSEN: Dr. Vivek Pinto.

DR. PINTO: Hi, everybody. Vivek Pinto, I'm the director for the Division of Neuromodulation and Physical Medicine Devices at the FDA and I've been here about 8 years.

DR. JENSEN: Thank you.

Dr. Lin Zheng.

(No response.)

DR. LOFTUS: Where's Lin? She must be here. She's on mute, apparently.

DR. JENSEN: Oh, okay.

DR. ZHENG: Oh, I'm sorry. This is Lin Zheng, can you hear me now? I am the division director for Division 5 A, that includes neurosurgical, neurointerventional, and neurodiagnostic devices.

DR. JENSEN: Thank you very much.

Dr. Christopher Loftus.

DR. LOFTUS: Good morning, Mary, thank you. Thanks to all the Panel members for helping us and thank you, Mary, for chairing this important session.

DR. JENSEN: Absolutely.

DR. LOFTUS: My name is Christopher Loftus, I'm a supravascular neurosurgeon. I've been working also at the FDA since 2017 and now I am the acting director of OHT 5.

DR. JENSEN: Thank you.

Dr. Patricio Garcia.

CDR GARCIA: Good morning, Dr. Jensen. My name is Patricio Garcia and I am the Designated Federal Officer for this meeting. Thank you.

DR. JENSEN: Thank you. So I'm going to circle back around.

Dr. Karen Anderson, are you on?

(No response.)

DR. JENSEN: And Dr. Stavropoula Tjoumakaris, I see you're here now. Could you introduce yourself, please?

DR. TJOUMAKARIS: Hello, hi. Sorry about that, it's my son's graduation today so I kind of -- yes. Hi, I'm Stav Tjoumakaris. I am a neurosurgeon from Thomas Jefferson University in Philadelphia, a Professor of Neurological Surgery, and I serve as the fellowship director for endovascular and cerebrovascular. Also clerkship director and associate residency program director.

DR. JENSEN: Thank you very much.

DR. TJOUMAKARIS: Thank you.

DR. JENSEN: One more time, Dr. Anderson.

(No response.)

DR. JENSEN: Okay, so we're going to move on and hope she joins us.

CDR Garcia, the Designated Federal Officer for this meeting, will make some introductory remarks.

CDR GARCIA: The Food and Drug Administration is convening today's meeting of the Neurological 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 discussion of today's meeting, members and consultants of this Panel who are special Government employees or regular Federal employees have been screened for potential financial conflicts of interest of their own as well as those imputed 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, during Session I, the Committee will discuss and make recommendations regarding the classification of topical refrigerants (vapocoolants), which are currently unclassified preamendment devices, to Class II (general and special controls).

During Session II, the Committee will discuss and make recommendations regarding the classification of acupressure devices, which are currently unclassified preamendment devices, to Class I (general controls).

During Session III, the Committee will discuss and make recommendations regarding the classification of electro-acupuncture stimulators, which are currently unclassified preamendment devices, to Class II (general and special controls).

Based on the agenda for today's meeting and all financial interests reported by the

Panel members and consultants, no conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208.

Elijah Wreh is serving as the Industry Representative, acting on behalf of all related industry. He is employed by Zimmer Biomet.

We would like to remind members and consultants that if the discussion involves 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 that they may have with any firms at issue.

A copy of this statement will be available for review and included as a part of the official transcripts. Thank you.

DR. JENSEN: Thank you very much. Now we will begin this meeting with the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel, to present data, information or views relevant to the meeting agenda.

CDR Garcia will now read the Open Public Hearing Disclosure Process Statement.

CDR GARCIA: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency during the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationships that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company or a group's payment of your travel, lodging or other expenses in connection with your

attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. Thank you.

DR. JENSEN: Thank you very much. We have only one Open Public Hearing speaker today. I would like to welcome Dr. Diana Zuckerman to address the Panel.

DR. ZUCKERMAN: Thank you very much. I'm Dr. Diana Zuckerman, President of the National Center for Health Research. Our center is a nonprofit think tank that scrutinizes the safety and effectiveness of medical products, and we don't accept funding from companies that make those products.

Today I'm speaking from my perspective as a scientist trained in epidemiology and public health, who left Harvard more than 30 years ago to come to Washington, D.C. to work in the House of Representatives. I worked as a congressional investigator for the subcommittee that conducted oversight over all of the Department of Health and Human Services, and that's when I first learned about the laws and regulations governing the FDA. I was responsible for several oversight hearings that attracted enormous media attention because we found that patients had been harmed when the FDA was not following the law pertaining to FDA regulation of medical devices.

As you all know, the law states that devices must be reasonably safe and reasonably effective. It's not exactly clear what reasonably safe or reasonably effective means, and often the FDA states that if they have reason to believe that similar devices are reasonably safe and reasonably effective, that's good enough. The special controls for Class II devices that the FDA has suggested for devices you're reviewing today and tomorrow provides some evidence that the devices will work as intended and will be reasonably safe, but the general controls for Class I devices do not.

Neurological devices are important and some of these devices are somewhat complex. Obviously, something called the Barf Band, which is one of the acupressure devices, is not a complicated device and they do sell for about $10. But if the goal is to prevent nausea and vomiting, and if the company wants to sell that product in the United States, shouldn't it be proven to work like any other neurological device? And some of these acupressure devices don't cost $10, some of them cost $20, they're $30 and some of them even cost a couple of hundred dollars.

Just because the risks are small should not make it okay for the FDA to let companies sell devices that are not effective if used as directed. The standards for medical devices should be higher than the "let the buyer beware" standards of dietary supplements, for example, which are basically nonexistent standards.

So, in looking at the data, I was reassured that there are randomized controlled trials on many of the devices that you're going to be talking about in the next 2 days, but there are many companies making many different versions of these devices. So the fact that some are shown to work in randomized controlled trials or other good studies doesn't mean that they all work and it definitely doesn't tell us what will happen when a new similar device, made either by these companies or made by other companies, gets on the market or wants to get on the market and whether that new device, which hasn't been tested, will be safe and will be effective.

The FDA has a reputation as the gold standard for safe and effective medical products, but that standard has been tarnished when patients are shown to be harmed as they have been in some recent documentaries and even in TV programs during primetime this week.

So I urge you, respectfully, to urge the FDA to up their game by regulating all these neurological devices as Class II and requiring the kind of meaningful evidence for new

devices that we would want for any device that we use either as health professionals, as patients, or as consumers.

Thank you very much for the opportunity to speak today and I really appreciate your work as Panel members and look forward to hearing what you have to say. Thank you.

DR. JENSEN: Thank you very much, Dr. Zuckerman.

Now Ms. Megha Reddy will present on the FDA classification and reclassification overview. Ms. Reddy, please proceed.

MS. REDDY: Hello, my name is Megha Reddy and I am a regulatory advisor within CDRH's Office of Product Evaluation and Quality. I will be providing you with a high-level overview of the medical device classification and reclassification processes which form the basis for the discussions over the next day.

The purpose of this Panel will be regarding the classification of devices that are currently unclassified. Specifically, for six preamendment devices, unclassified device types, the Panel will be asked to provide input to the FDA on the appropriate classification (Class III, Class II, or Class I) for each device type.

Let's start by explaining the different classes of medical devices. Devices are classified based on the controls necessary to mitigate the risks associated with the device type. Class I devices are only subject to general controls. Class II devices are subjected to both general and special controls. And Class III devices are subjected to general controls and premarket approval. These regulatory controls will be discussed in greater detail in the following slides. Importantly, a device should be placed in the lowest class whose level of control provides a reasonable assurance of safety and effectiveness.

Now we will go into a bit more detail about each of the classes. Again, Class I devices are those devices for which general controls are sufficient to provide reasonable assurance of safety and effectiveness of the device. General controls are basic

requirements that apply to all medical devices and are outlined in the Federal Food, Drug, and Cosmetic Act. Some examples include meeting established registration and device listing requirements; following good manufacturing practices; adhering to recordkeeping and reporting requirements; and ensuring that devices are not misbranded or adulterated. Most Class I devices do not require FDA premarket review prior to being marketed.

On the right-hand side of this slide you can see a few examples of Class I devices. These include hospital beds, ventricular needles and anvils used to form skull plates, and certain manual surgical instruments.

There is also an alternate pathway to determine that a device is Class I. Class I devices could also be devices that cannot be classified into Class III because they cannot -- they are not life-sustaining, life-supporting, or of substantial importance in preventing impairment of human health, and they do not present a potential unreasonable risk of illness or injury. And these devices cannot be classified into Class II because insufficient information exists to establish special controls to provide a reasonable assurance of safety and effectiveness.

Class II devices are those devices which cannot be classified into Class I because general controls by themselves are insufficient to provide reasonable assurance of safety and effectiveness of the device, and for which there is sufficient information to establish special controls to provide such assurance. There are many types of special controls, but some examples include performance testing, sterilization validation, and device-specific labeling requirements. These special controls, in combination with the general controls previously described, provide a reasonable assurance of safety and effectiveness for Class II devices. Examples of Class II devices include neurostimulators, aneurysm clips, and blood clot retrievers.

Typically, Class II devices require a premarket notification, generally referred to as a

510(k), prior to being marketed in the U.S. Within these 510(k) submissions, companies must also provide evidence demonstrating how special controls for the specific device type are met.

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

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

Now we will shift our focus to the classification process for the preamendments unclassified device types which will be discussed today and tomorrow. Before we walk through the process, here are a few quick definitions.

First, what is a preamendments device? A preamendments device is a device which was introduced into interstate commerce prior to May 28th, 1976 or the date of the enactment of the Medical Device Amendments to the Food, Drug, and Cosmetic Act.

An unclassified device is a preamendments device which was not classified by the original classification panels, therefore no classification regulation currently exists for these devices.

This brings us to the second purpose of this Panel meeting, to formally classify these unclassified devices. Please note that while these devices are not classified, they are currently brought to market through the 510(k) process.

These preamendments unclassified devices will be classified once the FDA has taken the following steps:

First, FDA will solicit input and a recommendation from the device classification Panel.

Second, FDA will publish the Panel's recommendation for comment along with a proposed rule outlining FDA's proposed classification for the device.

Finally, after taking into account public comments, FDA will publish a final rule classifying the device.

What we ask from the Panel today is to provide input on the classification of these unclassified device types and whether they should be classified into Class III, Class II, or Class I. The input should include an identification of the risks to health presented by the device; a discussion of whether the device is life-supporting, life-sustaining, of substantial importance in preventing impairment of human health or if it presents a potential unreasonable risk of illness or injury; a discussion of whether sufficient information exists to develop special controls, an identification of those special controls, and a discussion of whether general controls are sufficient by themselves.

Following this Panel meeting, FDA will consider all available evidence which includes the input received from this Panel and the public. The FDA will then publish a proposed rule in the *Federal Register* proposing classification of these device types and seeking public comment on the proposal. Finally, FDA will issue a final rule identifying the appropriate class.

If FDA determines that the devices can be appropriately regulated as Class I or Class II devices, the devices may continue to be marketed. However, if FDA determines that they fall into a Class III designation, a separate call for PMAs will also be published. Existing devices may remain on the market until a specified date, at which point a PMA should be submitted in order to continue marketing. If this PMA is not approved, the devices will be considered misbranded and must be removed from distribution.

Thank you. I hope this provided you with sufficient background to set the stage for the forthcoming discussions. Thank you for your time and attention.

DR. JENSEN: Thank you very much, Ms. Reddy, for your presentation.

Does anyone on the Panel have any questions for Ms. Reddy?

(No response.)

DR. JENSEN: Okay, so not seeing -- yes, Dr. Loftus.

DR. LOFTUS: Can I say something?

DR. JENSEN: Yes, please.

DR. LOFTUS: Mary?

DR. JENSEN: Yes, please.

DR. LOFTUS: Could I be recognized?

DR. JENSEN: Oh, yes, Dr. Loftus. The Chair recognizes --

DR. LOFTUS: I just want to talk briefly to the Panel members just to say that, you know, I was a Panel member for 15 years before I came to work here, so obviously the lens

is different. You might think that this is a simple thing and we just make a simple decision, but you can see, this process is very important to us. Each of these devices needs to be in the right place and codified in the right way. So as Megha just educated us all, it's a very important process and we're very respectful of the fact that it needs to be done and also that you took the time to come and help us with it. But I wanted to say it's important that everything gets in their right little slot.

DR. JENSEN: Thank you very much, Dr. Loftus.

Does any other Panel member have anything to say?

(No response.)

DR. JENSEN: So let's go ahead and move on then to the presentation on vapocoolant devices. We will now hear from Dr. Ozell Sanders, who will present on the vapocoolant medical devices.

Dr. Sanders, please proceed.

DR. SANDERS: Hello, my name is Ozell Sanders and I'm a mechanical engineer serving as a lead reviewer in the Division of Neuromodulation and Physical Medicine Devices within the Office of Neurological and Physical Medicine Devices in CDRH's Office of Product Evaluation and Quality.

In my presentation today I will be presenting information regarding the effort to classify vapocoolant devices under product code MLY. These devices are currently unclassified and we are looking for your thoughts and recommendations on the appropriate regulatory classification for these devices.

Here's the outline for today's presentation. These are the items that we will be discussing over the course of this presentation.

Vapocoolant devices have been widely used for many years to induce the rapid decrease of skin temperature. For example, the use of ethyl chloride dates back to the

second half of the 19th century. Vapocoolant devices encompass a family of devices used to rapidly apply a chemical to the skin which rapidly evaporates, subsequently inducing transient cooling of the skin.

The mechanism for chemical ejection and the formulation of these chemicals varies between specific products. For example, many devices are metal aerosol containers filled with one or more liquids, like ethyl chloride, which exists at low vapor pressure at room temperature. These liquids are sealed into a metal canister under high pressure. When pressure is applied to the nozzle it releases the seal, allowing the liquids to escape the canister and rapidly vaporize into droplets. Some devices spread the droplets out or focus them into concentrated streams in order to modulate the size of the targeted surface area.

The indications for use or IFU statement identifies the conditions and patient populations for which a device should be appropriately used. Vapocoolant devices are intended for the temporary relief and reduction of minor topical pain and swelling from sprains, strains, bruising, contusions, and minor injuries and in the management of myofascial pain, restricted motion, and muscle tension. In addition, it is used for pain reduction associated with hypodermic injections including venipuncture and vaccinations, and for minor surgical procedures such as incisions, sutures, and drainage of small abscesses. It is also used to reduce pain by topical application to intact mucous membranes in the oral cavity, the lips, and some minor open wounds. Most, but not all, of these devices are cleared for prescription use.

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

device. Since these devices are unclassified, there is no regulation associated with the MLY product code.

To date, a total of 25 510(k)s were cleared through the 510(k) pathway under the vapocoolant devices product code MLY. As stated previously most, but not all, of these devices are cleared for prescription use. Please refer to Section 2 of the Executive Summary for a complete list of cleared devices under product code MLY.

All of these devices are intended to induce rapid topical cooling with the most common intended use being some form of local anesthetic.

Mechanical and thermal stimuli activate nociceptors in the skin and subcutaneous tissues that stimulate A delta and C neural fibers that transmit neural signals via multiple pathways to the central nervous system, where these stimuli are further processed and perceived as pain. Vapocoolant sprays rapidly reduce the temperature of the skin and impede the stimulation of nociceptors to temporarily reduce the perception of painful stimuli.

Pain from minor injuries, injections, minor surgical procedures, minor wounds, and myofascial pain can be mitigated with ice, cool compresses, and topical analgesics. Oral medication options include non-steroidal anti-inflammatory medications and acetaminophen. Pain control for minor routine procedures is not necessary in all situations.

Pain secondary to myofascial and mild muscle pathology can be managed with heat-conveying modalities, injection of local anesthetics, active or passive stretching, therapeutic exercise, and the application of direct or indirect pressure via manual techniques.

We conducted a literature review to identify published information between January 1st, 2010 and December 31st, 2020, regarding the safety and effectiveness of vapocoolant devices. Searches were limited to publications in English and excluded conference proceedings and abstracts. Due to extensive research on vapocoolant devices,

many randomized controlled trials, or RCTs, were conducted and published in the last decade. Therefore, we limited the literature review to RCTs where at least one treatment arm used a vapocoolant device in the trial. A total of 35 articles reporting RCTs were selected for review based on the relevance to reported safety and/or effectiveness of these devices. I'll briefly summarize the main conclusions from our review of these articles.

The majority (71.4%) of these publications reported no complications or did not report an adverse event or safety risk with the use of the device. The remaining 10 RCT studies reported adverse events, which include numbness, erythema, swelling, bruising, blanching, sores, and other minor local skin reactions. These adverse events were mild in scope and severity. There is no evidence of a mortality risk from the use of these devices reported in the literature. The adverse events were transient or temporary and resolved soon after the cooling effect expired without the need for additional treatments.

The effectiveness of the device and the reduction of pain from routine procedures involved in needlesticks, such as vaccination, cannulation, and venipuncture, is supported by 22 of the 32 randomized controlled trials, in comparison with placebo-controlled or alternative treatments. However, 10 randomized controlled trials did not show effectiveness of topical refrigerants in such comparisons.

In summation, the adverse events found in the literature were transient or temporary and resolved soon after the cooling effect expired without the need for additional treatments.

Based on the clinical evidence derived from the systematic literature review, the benefit-risk profile of vapocoolant devices for the use of the reduction of pain from routine procedures involving needlesticks is favorable, with no serious adverse events or only minor transient skin reactions occurring.

The next three slides provide background information for medical device reports, or

MDRs. The MDR system provides FDA with information on medical device performance from patients, healthcare professionals, consumers, and mandatory reporters.

The FDA receives MDRs of suspected device-associated deaths, serious injuries, and certain malfunctions. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products.

MDRs can affect these to establish a qualitative snapshot of adverse events for a specific device or device type, and detect actual or potential device problems used in a real-world setting or environment.

Although MDRs are a valuable source of information, this passive surveillance system has limitations including underreporting; data quality issues like the potential submission of incomplete, inaccurate, untimely, unverified, or biased data. Limitations of MDR regulation or lack of MDRs does not necessarily mean that there are no problems, and it is not possible to definitively determine a causal relationship between the event and the device based on MDR data alone. And finally, the incidence or prevalence of an event cannot be determined from this supported system alone due to potential underreporting of events and lack of information about the total number of devices.

To further contribute to the benefit-risk assessment of vapocoolant devices, the Agency reviewed individual medical device reports, or MDRs, for this product code under the FDA's Manufacturer and User Facility Device Experience, or MAUDE, database. The Agency searched the MAUDE database to identify adverse events related to the use of vapocoolant devices under product code MLY entered between November 1st, 1989 and December 31st, 2020.

The search identified 15 relevant MDRs. Of the 15 reported adverse events, 10 were related to injuries reported by the manufacturer, voluntary reporter, and user facility. Noted injuries included burns, frostbite, seizure, asthma reactions, hallucination, and skin

irritation. Four of the reported adverse events were due to device malfunction, and one adverse event resulted in death due to intoxication from chloroethane, also known as ethyl alcohol, the active ingredient in this device.

The medical device recall database contains medical device recalls classified since November 2002. Since January 2017, it may also include correction or removal actions initiated by a firm prior to review by the FDA. The status is updated if the FDA identifies a violation and classifies the action as a recall and again, when a recall is terminated. FDA recall classification may occur after the firm recalling the medical device product conducts and communicates with its consumers about the recall. Therefore, the recall information and posting date identified on the database indicates the date FDA classified the recall and it does not necessarily mean that the recall is new.

Two Class II recalls have been identified in the medical device recall database with the product code MLY. Both of these recalls were voluntarily initiated by the Gebauer Company during 2007 and 2008. The first recall was initiated on April 17th, 2007 for six prescription use-only vapocoolant devices due to a fungus mold contamination identified during internal quality control sampling, specifically, during the 6-month stability testing the microbial limits from the total aerobic count. The recall was completed February 2nd, 2008.

The second recall was initiated on September 3rd, 2008, in response to a customer complaint which led to a corrective and preventive actions investigation. That revealed lots of Gebauer's fluro-ethyl had a defective gasket. No injury was reported as a result of the malfunctioning unit. The recalled product was discontinued because the valve supplier was unable to correct the issue without a major redesign of the valve which the company contended was not feasible from a business standpoint.

To determine the appropriate classification for vapocoolant devices, we have identified risks associated with these devices and possible mitigations for these risks. We'll

be asking the Panel for input on the lists of risks and mitigations.

To identify the risks of these devices, we used FDA's MAUDE database to identify MDRs and the information available to FDA regarding cleared devices. We also conducted the previously discussed literature review.

Here are the risk categories we've identified for vapocoolant devices:

- Pain or discomfort resulting from burns or blistering;
- Skin irritation resulting from burns or blistering;
- Thermal injury resulting from frostbite or burns particularly when used in combination with electrical cautery leading to ignition, leading to redness, blistering, and edema;
- Electrical shock resulting from electrical failure or malfunction; and
- Interference with other devices, which may cause unacceptable degradation in device performance leading to delayed or ineffective treatment.

Additional risks identified include device failure/malfunction leading to ineffective treatment, asthma as a result of an alleged response to the product or aerosol delivery system, as well as hallucination resulting from improper use of the device and subsequent inhalation toxicity.

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

This is a risk mitigation table which outlines the identified risks to health for this device type and the recommendation controls to mitigate the identified risk. To mitigate the risk of pain, discomfort, and skin irritation, we recommend labeling controls. And to mitigate the risk of thermal injury, we recommend nonclinical performance testing and

label controls. To mitigate the risk of electrical shock or burn, we recommend electrical safety testing. To mitigate the risk of interference with other devices, we recommend electromagnetic compatibility or EMC testing. To mitigate the risk of device failure and malfunction leading to ineffective treatment, we recommend nonclinical performance testing and labeling controls. And to mitigate the risk of asthma and hallucination, we recommend labeling controls.

Here is our proposed classification regulation for vapocoolant devices. Part (a) of the regulation defines the device as follows: A vapocoolant device is a cold therapy device intended for the temporary relief and reduction of minor topical pain and swelling. The device consists of a compressed low-vapor pressure liquid, which is rapidly sprayed onto the skin whereupon the contacted skin is transiently cooled through rapid evaporation. Furthermore, we are proposing these devices be classified as Class II devices with special controls.

Based on the identified risks and recommended mitigation measures, FDA believes that the following special controls would provide a reasonable assurance of safety and effectiveness for the vapocoolant devices under product code MLY:

1. Nonclinical performance testing must characterize the change in surface skin temperature control when the device is used as intended.
2. Nonclinical performance testing must demonstrate electrical safety and electromagnetic compatibility for powered devices.
3. Healthcare provider and patient labeling must include:
    a) Information on how the device operates and the typical course of treatment
    b) A warning that the device should not be used near an open flame, high heat or electric cautery devices
    c) A warning regarding the risk of frostbite or burns if the device is not used as

directed

d) A warning that if skin irritation persists, discontinue use of the product

e) A warning that the device should not be used by individuals with known allergies to product ingredients, as use by such individuals may lead to an allergic response including difficulty breathing

f) A warning that the device should not be directly inhaled, as this may be harmful or fatal

So this concludes our --

DR. JENSEN: Sorry, I don't hear anything. The audio's off.

MR. VEIZIS: That's okay, he did conclude the presentation.

DR. SANDERS: We thank you so much for your time and attention and your thoughtful feedback to the following Panel questions.

DR. JENSEN: Thank you very much for that excellent presentation.

I would like to recognize Ms. Veverly Edwards, who's come on the Panel now, and she's one of our representatives. Could you please introduce yourself, Ms. Edwards?

MS. EDWARDS: Hi. Yeah, my name is Veverly Edwards and I'm one of the consumer reps. I'm not sure what you want to know.

DR. JENSEN: Just wanted to know that you're here.

MS. EDWARDS: But I've been a panelist for neurological devices for about 2 years now. It's probably the third year. I am an instructor at the University of Memphis in Memphis, Tennessee and Southwest Community College here in Memphis, Tennessee.

DR. JENSEN: Thank you very much for introducing yourself.

I now would like to open the floor to the experts around the table to begin deliberating on the vapocoolant devices, considering your expertise, everything you have read in your panel packs and heard in today's Open Public Hearing, and from the

presentations. Anybody have something that they would like to say? I have a couple of questions myself.

So Dr. Dorsey, did you raise your hand?

DR. DORSEY: Yes, thank you, Dr. Jensen.

A question for the FDA presenter. My understanding is ethyl chloride's been previously used as an anesthetic and that it's been -- also, ethyl chloride has been used as a recreational drug and there's been at least case reports associated with death from people inhaling ethyl chloride. Can you comment on that? I didn't see any mention of that in your presentation.

DR. PINTO: Hi, this Vivek Pinto. Ozell, please answer the question if you have any additional information, but yeah, that type of use is considered off label for these devices. So you know, we really are looking to the literature for any additional information.

Ozell, could you comment any further?

DR. SANDERS: That is correct. And I do believe, in the presentation, we mentioned that there was one reported incidence of death in using the product. But again, as Vivek mentioned, that's an off-label use for this device.

DR. DORSEY: But just because something's off label doesn't mean it's not -- it means it's not safe. I mean, you'd have -- you know, if you have a chainsaw and you use it inappropriately, it's going to be unsafe. You need to take measures to make sure that a chainsaw is used appropriately and not inappropriately.

DR. PINTO: Yes, that's true. You know, that's why we also have warnings in the labeling. Also, would you recommend anything to us that we should include?

DR. DORSEY: Well, I would think at least a warning that it shouldn't be used inappropriately. I would also love to see what other drugs or devices have similar problems with recreational use and see what you've put in place to prevent that from happening.

You know, nitrous oxide. There are lots of drugs and devices that have significant adverse effects if used inappropriately and we should protect individuals from those risks.

DR. JENSEN: Thank you.

Dr. Lyden, I think you had a question. Yes.

DR. LYDEN: Yeah. Actually, Dr. Sanders, I have several questions for you, if you don't mind. The first one is thinking about that aspergillus contamination case, is shelf-life stability testing part of the general controls? Because you didn't mention that as a special control.

DR. PINTO: I don't believe it's part of the general controls, but that is an area that one would review in reviewing substantial equivalence to a predicate device in a 510(k).

DR. JENSEN: Well, I guess I mean, where is the requirement that the manufacturer do that type of testing? This one manufacturer caught the error, which is great, they were doing their testing, but where's the requirement that other companies have to do the same thing?

DR. PINTO: Well, the requirement would be when we review the device in comparison to the predicate. You know, it is something we could consider for the special controls, but we are also trying to link the -- you know, what we identified as the probable risk to health, to the special controls that were necessary.

DR. LYDEN: Okay. So my next question is similar. In one of the papers, or a couple of the papers that you referenced for us, there was this issue of the valve sticking open and the refrigerant uncontrollably continuing to exit. Is there device testing? Is that part of GMP or how do you know that these devices actually work? I didn't see where the requirement is that they have to show that their device doesn't break down after X number of uses.

DR. PINTO: Yeah, that's a good question. I should have said, too, in the previous

one. This is Vivek Pinto again. You know, there are quality systems regulations, too, that are part of the general controls that a firm would have to make sure that they do testing on their end. What we would require would be different for different devices, but we would generally look at the comparison to the predicate and it would include performance testing, too.

DR. LYDEN: Cool. Okay, great. And then my last question is most of the devices use ethyl chloride, but the way you wrote the definition of the vapocoolant, it just says a low vapor pressure fluid that gets ejected and cools the skin. So if somebody invents a brand new chemical and comes along with a spray that cools the skin and wants approval based on the predicate, they would -- they'd be allowed to go forward because it cools the skin. But what if that new chemical, you know, is a new chemical that may have other toxicity, where's the requirement that that chemical be shown to be nontoxic?

DR. PINTO: Yeah, that's a great question. This is Vivek Pinto again.

I'll say a little bit about the 510(k) pathway to clarify that, and certainly if Megha or Sergio want to chime in, please do. But what we'll first look at is whether there's a valid predicate device that the sponsor is proposing to compare their device to, then we'll look at the comparison for the indications for use and see whether there's a different indication or present the new intended use. And then following that is where we compare the technological characteristics.

And so if those aren't identical, which wouldn't be the case in your scenario, we would then determine whether the new technological characteristic would raise different questions of safety and effectiveness, and either if we did find that there were different questions, then it may not be appropriate for the 510(k) pathway and would either be subject to a De Novo or a PMA. But if there weren't different questions but concerns still for safety and effectiveness, they would still go down to the category for performance

testing needed to demonstrate substantial equivalence.

DR. JENSEN: Anybody else with any other questions?

Yes, Dr. Johnston.

DR. JOHNSTON: I just had a quick question about the labeling part. Looking at the data that was provided to us, that there is an increased risk in the oral mucosa and possibly an increased risk in those patients with diabetes or -- and I'm wondering if you could speak to the issue of whether there'd be some way to offer some more information --

DR. PINTO: Yeah, that's a great question. Ozell, can I invite you to answer that, if you have any other thoughts on additional warnings or controls?

DR. SANDERS: I actually missed part of the question. I don't know if I was the only one having trouble hearing that. Do you mind repeating it for me, please?

DR. JOHNSTON: I was hoping that you would speak to the issue of the potential increased risk to the oral mucosa and the potential increased risk for those patients with diabetes or --

DR. SANDERS: That's something that we haven't considered, I'm sure that we can take that into consideration and include that as part of the labeling, as we see fit.

DR. JENSEN: Yeah, that was the question I was going to ask, too, Dr. Johnston, and I was also going to add, my understanding is that the reasons for use included also minor open wound, and there was absolutely no data whatsoever about the device so that the material being used on an open wound -- and I just felt that, at least in the literature that was there, you know, there was an issue with a diabetic patient, and then the significant issue with the mucosal lesions, I think it was like 80%, seems to me that the open wound would also potentially carry some significant risk and there was just no data whatsoever in terms of open wounds whether they're minor or not. Would you comment on that? In other words, approving the device for something it's not even been tested on but in other

situations showed some harm.

DR. PINTO: Sorry, this is Vivek again.

I do realize, yes, there is the clearance for certain indications and these do go back quite a bit of way, so there are limitations also in the resources, we have to see the determinations. But we can certainly -- you know, we based our recommendations on what we did see in the literature as a body of literature, not necessarily a single article and -- but we can -- we're definitely open to other suggestions for other ways to control for probable risks and certainly open to any recommendations you have, if you see that that type of scenario does present a probable risk to health.

DR. JENSEN: Dr. Pilitsis, do you have something you want to say?

DR. PILITSIS: I did. Thanks, Dr. Jensen.

So I had two comments and a question or maybe it's two questions and a comment. The first was a point of clarification. Asthma and death complications are the ones that really resonated and were those cases of use in the oral mucosa?

DR. PINTO: Yeah, so I just have to look up one thing.

Ozell, if you can answer that, please do. I need to look up one document.

DR. SANDERS: I will have to double check, I apologize, I don't know off the top of my head. I do believe that information is present in more detail in the summary that was provided.

(Cross-talk.)

DR. PILITSIS: Yeah. Thanks, I just tried to do a quick search of it with the find function and wasn't able to ascertain that, so I think that would be helpful in terms of figuring out any controls that are used in the oral mucosa category.

My second point was in that summary document, I think one thing that resonated was in the pediatric incidences there was an issue when this was used with electrocautery

and so I don't know if there's any specifics on that. You know, I know in the operating room any time we use any betadine or ChloraPrep or Duraprep, we wait 3 minutes to decrease the fire burn risk, so I wasn't sure if there was any data available on that.

DR. PINTO: Thanks, Dr. Pilitsis. I don't think we have data available there, but I did look at the death report. What we have is pretty limited. From what I read, I don't believe that it was for the use for oral mucosa, it does look like the patient took the device home and then died of chloroethylene inhalation and -- or intoxication and there isn't any information on it.

DR. PILITSIS: Okay. So it may be off-label use of this device.

And then I'd just make what's a point of agreement with Dr. Jensen in regards to the open wound. You know, I think in terms of us putting controls on things, just understanding what literature is available and there isn't literature in that regard, probably, addressing the controls appropriately. Thank you.

DR. JENSEN: Any other panelists have anything they would like to add?

Yes, Dr. Galen.

DR. GALEN: Thank you, Dr. Jensen.

I would like to echo the comments on the oral application. But my question is more on the literature, it doesn't say anything about the duration of exposure and the relation to skin irritation, because a potential thing that could be added is they meet at those -- the duration in which the nozzle can expose the skin to the vapocoolant and I just would like to ask if that's -- if there's any data on that.

DR. PINTO: I believe there was data on what could be injurious for a certain use.

Ozell, I'm not sure if you know any other data that you reviewed that could answer that question beyond what we found. You know, for these executive summaries we did try to put in and summarize all the information we could find and then also give references at

the end and I know there's also limited time to review all those, but Ozell, did you find anything else on the duration of exposure?

DR. SANDERS: Not that I'm aware of, but I can certainly look into that information and get back to you after lunchtime, if that would help.

DR. GALEN: Thank you. Because potentially what I think with skin irritation and other issues is the exposure time and if that is limited, then maybe some mitigation of that. Thank you.

DR. PINTO: And I would say one more comment on that. You know, during the substantial equivalence determination, that is one characteristic we would look -- or a technological characteristic and directions for use. So that is something that, I guess if it presented a probable risk to health that wasn't controlled, I would think that we would see some of that in the adverse event reporting to quite a degree.

DR. JENSEN: Thank you.

Dr. Cooper, I think I saw you wave your hand. You're muted.

DR. COOPER: Yeah, I'm sorry, I was just trying to get to the mute button.

So I just had a point about -- most of the cooling is done through fluids that have -- that might be flammable, typically something in the alcohol family, and I think there should be at least some review or some note about the flammability risk.

DR. JENSEN: Thank you very much.

Yes, Dr. Kennedy.

DR. KENNEDY: I have a question and it might be an ignorant comment, but when I look at the indications for use, I see sprains, strains, management of myofascial pain, restricted range of motion, muscle tension. When I looked through the 510(k) submissions, all but two of them either mention sports injuries or myofascial pain as the indication. The two that did not, one was for topical teeth and the other one was relief of minor localized

pain, so it's pretty broad. Yet, when I looked at the literature reported, it is almost ubiquitously about injection, you know, reducing pain associated with injection.

There is one study on an ankle that they did do a control to it and it's the last reference from Dr. Gur et al. I don't know how you do a real placebo control in this group and yet the difference is 1.56, that's not reaching the minimal clinical important difference. So I do have some questions about the indications for myofascial pain in particular when I see no references for them.

DR. JENSEN: Thank you.

Any comments from the FDA? Yes.

DR. PINTO: Yeah, so one thing is a sponsor would propose their indications for use and we would go through the process premarket to determine whether it's substantially equivalent. Postmarket, though, there are certain uses that we would see show up in the literature or in our MDR reports and so that's -- you know, it is something to consider for your question. There may be either off-label uses or uses that are clear that there's more information about that we learn about in the postmarket setting.

DR. JENSEN: Any other questions from the panelists?

(No response.)

DR. JENSEN: Okay, so why don't we move on to looking at the questions? So we're going to focus our discussion on the FDA questions. Copies of the questions can be found in your electronic documents and on the FDA website. I want to remind the Panel this is a deliberation period among the Panel members only. Our task at hand is to answer the FDA questions based on the data in the panel packs, the presentations, and the expertise around the table.

I also want to recognize that Dr. Roberto Ortiz-Aguayo is with us. Could you please introduce yourself, as you're a panelist?

DR. ORTIZ-AGUAYO: Hi. I'm Roberto Ortiz-Aguayo. I'm associate chair of the department of psychiatry and behavioral sciences at Children's Hospital, Philadelphia. I'm a pediatrician and a child psychiatrist, and my area of specialty is psychosomatic medicine.

DR. JENSEN: Thank you very much for joining us.

So Dr. Ozell Sanders will now read FDA Question Number 1, there are three questions in total. Dr. Sanders, please proceed.

DR. SANDERS: Thank you. All right. So I just want to make sure everyone can see my screen with the questions. All right.

So the FDA has identified risks to health for vapocoolant devices. These identified risks include pain or discomfort, skin irritation, thermal injury.

Sorry, looks like my slide is frozen here. There we go.

Additional risks include electrical shock or burn, interference with other devices, device failure and malfunction leading to ineffective treatment, asthma, as well as hallucination.

So we would like to ask the Panel to please comment on whether you agree with the inclusion of all the risks in the overall risk assessment of vapocoolant devices under product code "MLY." In addition, please comment on whether you believe that any additional risks should be included in the overall risk assessment of these devices.

DR. JENSEN: Okay, so let's go back to the Panel members, if I can see all my Panel members, since I'm probably going to ask people to raise their hands. Can we put everybody back on the screen? Thank you so much.

So panelists, I can summarize this from what we all just discussed, but I think do we all agree with the inclusion of all the risks and the overall risk assessment as they are listed?

(Show of hands.)

DR. JENSEN: I see a show of hands, people would say yes. Okay, great.

In addition, please comment on whether you believe that any additional risks should be included in the overall risk assessment of these vapocoolant devices. I will just try to summarize, anybody can correct me if I'm wrong. Some of the other risks that were discussed was the risk that could be associated with the use in patients with diabetes or other types of peripheral neuropathies, use on the oral mucosa, use on an open wound.

Other issues that were of concern were better instructions on use of the material when electrocautery is being used, labeling for potential death, if inhaled, and let's see, adding dose and duration recommendations in the directions for use and also including in this the flammability risk of the material. Did I hit it all, do you think? Okay.

So let's go on to the next question.

DR. DORSEY: Dr. Jensen.

DR. JENSEN: Oh, yeah. Sorry.

DR. DORSEY: I want to elaborate on the risk of abuse. So I just put an article in the chat for the panelists, and the conclusion of the article just published this year says, "The propensity for addiction and adverse effects of ethyl chloride are under-appreciated due to lack of awareness in public and healthcare professionals. We wish to raise awareness among the physicians regarding its rising trend of abuse as an inhalation agent due to ease of availability and neuro-stimulatory effects."

Their last sentence is, "Raising public awareness, as well as improving vigilance on the sale of these products will help in reducing the burden of abuse." You know, these appear to be used predominantly for sports injuries, which would be targeting a population of young adults who might be at higher risk for abuse. Within 5 minutes I found at least three reported deaths associated with ethyl chloride. I think there should be significant thought and consideration beyond just warnings to -- how to prevent abuse of ethyl chloride, you know, whether to make it smell terrible or otherwise unattractive, there can

be lots of things done that are done for similarly dangerous chemicals.

DR. JENSEN: Thank you, Dr. Dorsey.

Any other comments?

(No response.)

DR. JENSEN: Shall we go on to the next question?

DR. SANDERS: Dr. Jensen, is it okay to move on to the next question?

DR. JENSEN: Yes, I think for now it's okay to move on to the next question.

DR. SANDERS: All right.

DR. JENSEN: And who is reading that? That's not me, right?

DR. SANDERS: No, no, that's me. I'm trying to make sure I've got the right screen here. All right. Can you confirm that you can see the question on the screen? Yeah, okay. Great.

So Section 513 of the Food, Drug, and Cosmetic Act states that a device should be Class III if:

- insufficient information exists to determine that general controls are sufficient to provide a reasonable assurance of its safety and effectiveness or that the 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 if the device presents a potential unreasonable risk of illness or injury.

A device would be considered Class II if:

- general controls by themselves are insufficient to provide a reasonable assurance of the safety and effectiveness, AND
- there is sufficient information to establish special controls to provide such assurance.

A device should be considered Class I if:

- the general controls are sufficient or provide a reasonable assurance of the safety and effectiveness, OR
- insufficient information exists to:
  - determine that general controls are sufficient to provide a reasonable assurance of the safety and effectiveness, OR
  - establish special controls to provide such assurance, BUT
    I. 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
    II. does not present a potential unreasonable risk of illness or injury.

The FDA believes that general controls by themselves are insufficient to provide reasonable assurance of safety and effectiveness, and 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. As such, FDA believes that Class II is the appropriate classification for vapocoolant devices.

The following is a risk/mitigation table which outlines the identified risks to health for this device type and the recommended controls to mitigate the identified risks. The identified risks include pain or discomfort which the recommended mitigation measure includes labeling; skin irritation, which includes bruising, numbness, swelling, which can be addressed through labeling; thermal injury including sores, frostbite, burns, and skin blanching which we believe can be mitigated through nonclinical performance testing and labeling; electrical shock or burn, which we believe can be mitigated through electrical safety testing; interference with other devices, which we recommend electromagnetic compatibility testing; device failure/malfunction leading to ineffective treatment, which we

believe nonclinical performance testing and labeling are appropriate mitigation measures; asthma, as well as hallucination, which we both believe can be mitigated through appropriate labeling.

As such, please discuss whether the identified special controls for vapocoolant devices appropriately mitigate the identified risks to health and whether additional or different special controls are recommended. The proposed special controls include the following:

1. Nonclinical performance testing must characterize the change in skin surface temperature control when the device is used as intended.
2. Nonclinical performance testing must demonstrate electrical safety and electromagnetic compatibility for powered devices.
3. Healthcare provider and patient labeling must include:
    a. Information on how the device operates and the typical course of treatment.
    b. A warning that the device should not be used near an open flame, high heat or electric cautery devices.
    c. A warning regarding the risk of frostbite or burns if the device is not used as directed.
    d. A warning that if skin irritation persists, discontinue use of the product.
    e. A warning that the device should not be used by individuals with known allergies to product ingredients, as use by such individuals may lead to an allergic response including difficulty breathing.
    f. A warning that the device should not be directly inhaled, as this may be harmful or fatal.

Please comment on the proposed question. Thank you.

DR. JENSEN: So can we go back to the screen? Thank you very much.

Okay, panelists, would anybody like to comment on Question 2?

Yes, Dr. Lyden.

DR. LYDEN: So obviously, to me, it's a Class II designation. I agree with the FDA's thought on that. And the warnings encompass our discussion pretty well. I want to -- except for the diabetes, you know, there should be a warning not to be used in patients with diabetes or other conditions characterized by poor skin healing.

But going back to Dr. Dorsey's suggestion, is it possible to require admixture with a substance that would make it an unpleasant smell so that people wouldn't inhale it, is that possible?

DR. PINTO: Dr. Jensen, am I allowed to comment right now? I know this is supposed to be for the Panel.

DR. JENSEN: Yes, please go ahead and speak to that.

DR. PINTO: You know, it's certainly possible for a company to propose that. In our review, we tried to look at the literature and the MDRs that we see to see collectively what are the probable risks to health, what's going to happen for on-label use, and that's why we also recommend warnings, contraindications, for off-label use. That's a very interesting suggestion that Dr. Dorsey had. But as far as making it a requirement, we can certainly consider that if you recommend that, but we'd also have to think about what are the implications for the devices that are already cleared, is that really a probable risk where we need to have actually the technological characteristics changed in order to have the devices cleared.

DR. LYDEN: Well, okay, so that's very helpful because I think I would personally like to see FDA at least require studies or surveillance or data. I didn't replicate the search, but Dr. Dorsey said he found case reports of deaths and overdoses and just thinking back on my own emergency department experience, these things are abused and it would be worth

trying to get a handle on the incidence and maybe make some changes.

DR. PINTO: Yeah, it's definitely something to consider. You know, again like when we did our search we tried to focus on what was relevant for the on-label use for devices, but yeah, that's a good comment.

DR. JENSEN: Dr. Ortiz-Aguayo.

DR. ORTIZ-AGUAYO: I'm also wondering in terms of the labeling if -- for labeling for consumers that may be non-healthcare providers, if they use a pictorial, a pictorial approach for some of the dangers like flammability, like risk of poisoning, risk of alteration or mental status --

(Audio malfunction.)

DR. ORTIZ-AGUAYO: -- may be a way to try to mitigate that risk, as well.

DR. JENSEN: Dr. Cooper, did you have something you want to say?

DR. COOPER: Yeah, two things, actually. One, I think you probably need a hypoallergenic version for some individuals that are sensitive to smells and things like that, like chemical, so people that have disabilities related to that, we want to make sure and that might require maybe a prescription.

And then the other thing, there are samples, for example, benzene, which is used in gasoline, you know, the difference between gasoline and benzene is that gasoline has an additive to make it have color and also to smell, so people can see it and they can smell it and it gives a rather kind of obnoxious smell on purpose. And so I think that's -- that seems like a good approach to be used here as well, right, maybe -- so that would be less likely to be abused. I don't know if that has to be a requirement, if it can be a recommendation to -- or feedback to give to companies that are applying to use this.

DR. JENSEN: Very good.

DR. COOPER: And then also if there's a hypoallergenic version that wouldn't include

that, for example, for people that have sensitivities to smell, right, maybe that would require different controls.

DR. JENSEN: Okay. So I guess a couple other things I heard, too, that I was going to touch back on was for potential special controls would be what Dr. Lyden was talking about, which is shelf-life testing for contamination and also performance, device testing for quality control for the device failure.

The other question that was brought up that we would probably want us to address would be what happens if a company comes up with a similar device but the chemical is not ethylene chloride, that would have to actually be investigated and not necessarily be 510(k) since it's truly a different material and you have to prove that it's not dangerous.

Any other comments?

DR. PILITSIS: Dr. Jensen, this is Julie Pilitsis.

You know, I've really been swayed by Dr. Dorsey's points and just thinking about it, I have some of these in my cabinet and we use them for sports injuries, and I think with the routine labeling, you know, to keep out of the way of children, I think that it has to go one step further because I would just kind of ignore that and think it was about the flammability of the device, so I think the potential for abuse needs to be pointed out.

And I also wondered, and I don't know how or why this happens, so I'm sure you could shed light, but when I go buy cold medicine at the grocery store I have to give my license, that's a means of tracking this, is that FDA's purview to do something like that or is that not?

DR. JENSEN: Dr. Pinto or -- would you like to answer that? Or Dr. Sanders?

DR. PINTO: Yeah, I was trying to find the mute button. I believe that these were prescription-only devices, right? On label. Right, Dr. Sanders?

DR. SANDERS: Sorry, had to unmute myself. Yes, they are prescription use.

DR. PILITSIS: So then potentially there is a means to track them if they're prescription use somehow.

DR. MEZU-NWABA: Hi, this is Dr. Nina Mezu-Nwaba, I'm the deputy office director for Office of Neurological and Physical Medicine Devices. I understand exactly what you're saying about the -- about showing your driver's license at the pharmacy. I think that is for some of the restricted medications like Sudafed, which we have documented articles and literature on abuse of those ingredients, so most people are required to show their driver's license so that we can dispense a limited amount that period.

So as this goes on, if we find out that this falls into that category, the Agency would consider that and we could put them on restricted. But those are mostly over-the-counter medication, but from what I understand from Dr. Pinto and Dr. Sanders, this is going to be prescription use only.

Am I correct, Dr. Pinto?

DR. PINTO: Yes, that's what they're cleared for.

DR. MEZU-NWABA: Okay. Yeah, so this is prescription use only, so they'll only be able to get access to those if they have a prescription. But what you're talking about, I know exactly what it is, is the Sudafed, Sudafed is over the counter, so it's not prescription only, but we have restricted amounts that we dispense per period. I hope that answers your question.

DR. JENSEN: Dr. Loftus.

DR. LOFTUS: Yeah. Thanks, Mary.

This is all a fascinating conversation, we're so grateful to the members of the Panel for bringing it up. I just want to circle back to the first principle a little bit and that is we're not discussing at the present time a device and its marketing application. We're here discussing legally marketed devices that just weren't ever classified because of their history

and trying to assign a classification, so every discussion about special controls is obviously very pertinent.

In addition, as was pointed out by Megha Reddy in the first presentation, we do have a robust postmarket surveillance process in which we look for things such as you're all discussing today, and when things look like they're going off the rails, we do our best to do something about that. So do be assured that this is not the only time when we have a chance to prevent patient harm, that's what I'm trying to say. Thank you.

DR. JENSEN: Thank you very much for that observation and clarification.

Any other panelists -- one other thing I will say is, that was also brought up in the discussion, was to add dose and duration recommendations in the instructions for use and again, there was also the question of all those indications for myofascial pain, that that's not really been adequately explored in the literature and whether or not that should actually be considered a diagnosis for which it would be off-label use. So those are the things that I have written down that we've discussed in our conversation.

Does anybody else have anything else they want to bring up at this time?

(No response.)

DR. JENSEN: Okay, so we'd like to move on to the third question.

DR. SANDERS: Okay. So for the last question that we'd like to present to the Panel, please discuss whether you agree with the FDA's proposed classification of Class II with special controls for vapocoolant devices. If you do not agree with the FDA's proposed classification, please provide your rationale for recommending a different classification.

DR. JENSEN: Thank you.

Can I see the Panel again, please? All right, so panelists, can we please vote as to whether or not we believe that the Class II classification with the special controls that we have outlined to the FDA, is this an appropriate classification for this device?

Let's see. Dr. Johnston.

DR. JOHNSTON: Yes.

DR. JENSEN: Dr. McDavitt.

DR. McDAVITT: Yes.

DR. JENSEN: Dr. Galen.

DR. GALEN: Yes.

DR. JENSEN: Dr. Kennedy.

DR. KENNEDY: Yes.

DR. JENSEN: Dr. Ortiz-Aguayo.

DR. ORTIZ-AGUAYO: Yes.

DR. JENSEN: Dr. Dorsey.

DR. DORSEY: Yes.

DR. JENSEN: Dr. Cooper.

DR. COOPER: Yes.

DR. JENSEN: Dr. Lyden.

DR. LYDEN: Yes.

DR. JENSEN: Am I missing anybody else that's not on my picture here?

Dr. Pilitsis. Yes, no? Yes. Okay, thank you.

So the Panel agrees that this is an appropriate device for classification in Class II with special controls.

DR. LOFTUS: Great. Mary, could you ask Dr. Edwards? I'm not sure. Veverly Edwards.

DR. JENSEN: Dr. Edwards. Dr. Edwards? Ms. Edwards.

MS. EDWARDS: Oh. Oh, okay. Yes.

DR. JENSEN: And I guess Mr. Wreh. Are you voting members?

MR. WREH: No, not really.

MS. EDWARDS: I don't think we are.

MR. WREH: We're not, no.

DR. LOFTUS: My apologies, I didn't --

DR. JENSEN: That's okay, that's okay.

All right, so I think we've answered all the questions. Anybody have any last comments?

MR. WREH: Well, Dr. Jensen, I think I have one question but I'm not sure if Vivek or Dr. Sanders answered my question. I would like them to clarify if the device would be prescription only or OTC. I think that was clarified by Dr. Sanders, I'm not sure.

DR. JENSEN: I believe it's prescription only. Is that correct, Dr. Sanders?

DR. SANDERS: I believe it will be prescription use only, but I think Dr. Johnston, you mentioned that in the Executive Summary we state that most of the devices are prescription. I believe there are some minor accessory components that were cleared for OTC, but it's my understanding that these would be prescription use.

Vivek, is that accurate?

DR. PINTO: Yeah, I believe that these were for prescription use. I'll take another look, too.

DR. JENSEN: Yes, I think we would -- we can go around with the panelists, but I believe the panelists are of the understanding that this is a prescription item and should remain as such.

DR. DORSEY: These vapocoolant devices are prescription only? Like, the canister that they're spraying is prescription only?

DR. JENSEN: That's what we're trying to determine.

DR. PINTO: Can we get back to you after the break or one of the breaks?

DR. JENSEN: Yes, we can do that. It's now 10:30 and we actually can move on because we didn't have much in the way of comments in the Open Public Hearing session, is everybody okay with us moving on to the second device?

(No response.)

DR. JENSEN: Okay. So we will now go forward with the presentation on the acupressure devices and we will now hear from Dr. Mary Keszler, who will present on acupressure devices.

Dr. Keszler, please proceed.

DR. KESZLER: Good afternoon. My name is Mary Keszler and I am a medical officer in the Division of Neuromodulation and Physical Medicine Devices within the Office of Neurological and Physical Medicine Devices in CDRH's Office of Product Evaluation and Quality.

Today I will be presenting information regarding the effort to classify acupressure devices under product code MVV. These devices are currently unclassified and we are looking for your thoughts and recommendations on the appropriate regulatory classification for these devices.

Here is the outline for today's presentation. These are the items that we will be discussing.

Acupressure devices are used to apply pressure to the Pericardium (P6 or PC6) acupuncture points on the inner wrist. Application of consistent pressure at this point is applied through elastic or via a wristband, strap, or adhesive strip. A raised wooden or plastic bead or button is often embedded within the band, strap, or strip, which creates a resistive force against the inner wrist. In some devices the amount of pressure can be adjusted.

Acupressure devices are used in the treatment of nausea or emesis due to causes

including motion sickness, pregnancy, chemotherapy, and post-operative anesthesia. These devices are cleared for over-the-counter use.

Acupressure devices are a preamendments, unclassified device type. This means that this device type was marketed prior to the Medical Device Amendments Act of 1976. It was not classified by the original classification panels. Currently, these devices are being regulated through the 510(k) pathway and are cleared for marketing if their intended use and technological characteristics are substantially equivalent to a legally marketed predicate device. Since these devices are unclassified, there is no regulation associated with the MVV product code.

To date, there have been 11 acupressure devices cleared through the 510(k) pathway under the MVV product code, the first clearance occurring in 1990 and the last in 2020. All 11 devices are indicated for over-the-counter use. Please refer to Section 2 of the Executive Summary for a complete list of cleared devices under product code MVV.

The vast majority of cleared acupressure devices are intended to treat nausea. Nausea is an unpleasant sensation of needing to vomit and can occur independently or accompany gastric emesis.

The pathophysiology of nausea involves a disturbance of the normal rhythmic three-cycle-per-minute gastric myoelectrical activity controlled by the enteric brain neurons and the autonomic nervous system innervating smooth muscle cells of the gastrointestinal tract.

Vomiting is reflexive emesis activated by neuronal stimuli responsive to chemoreceptor triggers in the brain. Five principal neurotransmitter receptors have been found to mediate vomiting: M1 muscarinic, D2 dopamine, 5HG3, H1 histamine, and NK1 neurokinin receptors. Emesis occurs upon relaxation of the gastric and esophageal sphincter, and contraction of the proximal small bowel and abdominal muscles.

The management of nausea and vomiting primarily relies on drug treatment in

standard practice. Anti-emetic and prokinetic medications are useful in acute and chronic nausea and vomiting and include prochlorperazine, metoclopramide, domperidone, erythromycin, bethanechol, and seratonin antagonists. Other drug classes used to treat nausea and vomiting symptoms include antidepressants, which can be used when other anti-nausea drugs are ineffective.

Gastric electrical stimulation via implanted electrodes have been applied to select patients who are refractory to conventional therapy for nausea and vomiting. However, currently this is not an approved indication for use and the device is available in the United States only for humanitarian use.

Surgical options for the treatment of nausea and vomiting include gastrostomy, pyloroplasty, jejunostomy, and gastrectomy in patients with diabetic, post-surgical, and idiopathic gastroparesis, but these treatments have not been studied under well-controlled conditions, they remain options of last resorts.

We conducted a literature review to identify any published information between January 1st, 2010 and December 31st, 2020 regarding the safety and effectiveness of acupressure devices. Searches were limited to publications in English and excluded conference proceedings and abstracts.

A total of 28 articles were selected for review based on their relevance to the reported safety and/or effectiveness of these devices. Twenty-six were randomized controlled trials while the remaining two were prospective cohort studies. I will briefly summarize some of the main take-home points from each of these review articles.

Of the 28 studies reviewed, five reported on adverse events associated with acupressure devices. Safety outcomes reported in these studies include redness, swelling, tenderness, bruising, paresthesia, feeling of acupressure wristbands tightness, itchiness, discomfort, and pain.

Overall, 18 of the 28 studies, representing 64%, reported a statistically significant prevention or reduction in nausea and/or vomiting with the use of acupressure wristbands with a p-value less than 0.05.

In summation, the adverse events found in the literature were all mild in nature and resolved after removal of the acupressure wristbands without additional treatment. Clinical evidence from the published literature shows mixed results for the effectiveness of acupressure wristbands in the prevention or reduction of nausea and vomiting. As a result, it can be concluded, based on the peer-reviewed medical literature, that acupressure wristbands are safe and more effective in some patients than others.

The next three slides provide background information for medical device reports or MDRs. This information was summarized previously in the presentation for vapocoolant devices under product code MLY.

To further contribute to the benefit-risk assessment of acupressure devices, medical device reports were reviewed. The Manufacturer and User Facility Device Experience, or MAUDE, was reviewed for the acupressure devices cleared under product code MVV between January 1st, 1991, when the earliest reports would've been filed, to December 31st, 2020. No MDRs were reported.

This slide provides background information for recalls in the medical device recall database. This information was summarized previously in the presentation for vapocoolant devices under product code MLY.

One Class II recall has been identified in the medical recall database. Psi Bands acupressure and acustimulation wristbands were recalled in 2007 because the firm was marketing their devices before its 510(k) submission received clearance.

To determine the appropriate classification for acupressure devices, we have identified risks associated with these devices and possible mitigations for these risks. We

will be asking the Panel for input on the list of risks and mitigations. To identify the risks of these devices, we used FDA's MAUDE database to identify MDRs and the information available to FDA regarding cleared devices. We also conducted the previously discussed literature review.

Here are the two risk categories we've identified for acupressure devices:

Pain or discomfort. This can result from bruising, swelling, and tenderness under the wristband and at the pressure points, particularly if applied too tightly.

Skin irritation. This can result from improper cleaning and from pressure or contact with the wristband.

We propose that these risks will be sufficiently addressed by general controls and do not require special controls as part of the device regulation process.

Here is our proposed classification regulation for acupressure devices. Part (a) of the regulation defines the device as follows: An acupressure device is used to apply pressure to the Pericardium 6 (P6 or PC6) acupuncture points on the inner wrist(s) for the relief of nausea resulting from motion, pregnancy or morning sickness, postoperative anesthesia, or chemotherapy. Application of consistent pressure at this point is applied through elastic or applied force via a bead or button embedded in a wristband, strap, or adhesive strip.

Furthermore, we are proposing these devices be classified as Class I exempted devices with general controls.

This concludes our presentation. Thank you so much for your time and attention and your thoughtful feedback on the following panel questions.

DR. JENSEN: Thank you very much, Dr. Keszler, for that presentation.

I would like to open the floor to the experts around the table to begin deliberating on acupressure devices considering everything you've read in your panel packs and heard in today's Open Public Hearing and from the presentations. Who would like -- does anybody

have any comments?

Dr. Lyden.

DR. LYDEN: Well, I have a question, Dr. Keszler. You quoted out of the 28 papers a majority showed a statistically significant reduction in symptoms, but how many of those studies had controls, had placebo controls?

DR. KESZLER: I would have to go back to the Executive Summary to delineate, which if I recall the numbers correctly, of the 28 articles 26 were randomized controlled trials and two were prospective trials, but I would have to -- I could look back at the Executive Summary to make that clarification for you.

DR. LYDEN: Okay, so your recollection -- and of course, take all the time you need to re-review, but so your recollection is that some of these trials did actually have controls because the way the summary is worded, it sounds like the statistical significance was achieved pre- and post-use of the device, not post-use compared to a control device.

DR. KESZLER: I'll take a look at the Executive Summary, that way I can give you some more information.

DR. LYDEN: All right. Thank you very much.

DR. JENSEN: Yeah, Dr. Lyden, I know like for -- the one I was pretty interested in was the chemotherapy use and that was one that had five studies where they actually compared it to a sham wristband device and there was no statistically significant difference. And I think that was the one indication that seemed to have the -- I guess the least efficacy when you look at the -- when you actually look at the randomized controlled trial based against a sham. So that brings up one question as to whether or not the indications on labeling for use can eliminate some of the indications for use or indicate that there's not strong evidence that for this particular use, it would be clinically beneficial.

One question I also have is in the instructions for use, is there a way to indicate the

placement of the device? The reason I bring that up is you talk about it being over the Pericardium 6, which I'm not an acupuncturist, I really don't know where Pericardium 6 is, but I do know that if you place a device like this over the radial artery or the nerve, you may end up getting a blue hand or a nerve palsy and so is there a way to actually label it in such a way as to where the device needs to be placed in addition to indicating that it should be immediately removed if certain features such as blanching of the hand or numbness of the hand or weakness occurs?

DR. PINTO: Hi, this is Vivek Pinto.

Yes, the directions for use is -- you know, that is something that we review when we review 510(k)s for these and certainly that's something that all predicate devices, like I guess, new devices would have, if they were to be substantially equivalent to the predicate devices. But that is something -- you know, we can take that comment back to see if there's better wording, I guess, for the layperson.

DR. JENSEN: Would that make it a special control or can that still be done under general control?

DR. PINTO: That's a good question.

DR. JENSEN: Because if it's special control, if I'm understanding correctly, then that makes it a Class II?

DR. PINTO: Yeah. No, you're correct. Yeah. So can I invite Sergio to answer, help answer the question?

DR. JENSEN: Absolutely, yes.

MR. DE DEL CASTILLO: This is Sergio de del Castillo, I'm the Acting Associate Director for Policy in OHT5. So I just wanted remind everyone that for Class I products, as part of the labeling general controls, adequate directions for use are required, so that would be a necessary element of the labeling for the product.

DR. JENSEN: As a general control, not a special control?

MR. DE DEL CASTILLO: Correct.

DR. JENSEN: Other Panel members, do we have any other questions from the other panelists?

Yes, Dr. Galen.

DR. GALEN: Thank you, Dr. Jensen, for bringing up the placement because that was one of my comments in a direction, but I also think in the identified risk there should be a risk of continued experience of nausea and directions on how the individual needs to proceed in that situation. So those are my comments, thank you.

DR. JENSEN: Thank you, Dr. Galen. So if I understand you correctly, it would be a labeling such as "if nausea persists, then this."

DR. GALEN: That is correct, yes.

DR. JENSEN: Thank you very much.

Any other panelists?

Dr. Dorsey.

DR. DORSEY: Thank you, Dr. Jensen.

For Dr. Keszler. Was there any assessment of publication bias done in your review? That, you know, only more favorable studies were published as opposed to unfavorable.

DR. KESZLER: I unfortunately am not -- I don't have that information, but we did review all of the literature that met our criteria, both randomized and prospective trials, so we tried to catch the literature that was representative of what we were looking at.

DR. JENSEN: Thank you, Dr. Keszler.

Any other panelist questions at this time?

(No response.)

DR. JENSEN: I don't see any other questions, so let's go ahead and focus our

discussion on the FDA questions. Copies of the questions can be found in your electronic documents on the FDA website. I want to remind the Panel that this is a deliberation period among the Panel members only, our task at hand is to answer the FDA questions based on the data in the panel packs, the presentations, and the expertise around the table.

Dr. Keszler will now read FDA Question Number 1, there are three questions in total.

(Off microphone response.)

DR. JENSEN: Dr. Keszler, I think you're muted.

DR. KESZLER: Thank you for that. I'll try this again.

FDA has identified the following risks to health for acupressure devices: pain or discomfort and skin irritation. Please comment on whether you agree with inclusion of all the risks in the overall risk assessment of the acupressure devices under product code "MVV." In addition, please comment on whether you believe that any additional risks should be included in the overall risk assessment of these acupressure devices.

DR. JENSEN: Okay, I think I'll take that for the Panel because I think we discussed that, and it seems that the major issue is one of appropriate placement so that there is not compression of vascular or neurological structures that could result in injury to the limb, to the hand.

Anybody else on the Panel have anything to add there? Okay.

MS. EDWARDS: Is there any risk of infection?

DR. JENSEN: So Dr. Keszler, I think that in the information that I saw there was skin irritation but no evidence of infection, is that true?

DR. KESZLER: That's what we have found in our search.

DR. JENSEN: I guess one other question would be, since I don't know what the materials are made of, is there also potential for allergic reaction to the materials which should also be included? I would think if a patient is allergic to any of the components, it

shouldn't be used.

Dr. Cooper, you raised your hand.

DR. COOPER: Yeah, I was going to -- you actually kind of jumped the -- beat me there to the punch about allergic reactions. The other element, also recommend not for use with open wounds.

DR. JENSEN: Yeah, very good points. So not to place the device on an open wound.

Dr. Galen, did you say something?

DR. GALEN: Yes, about the continuant experience of the nausea, that sort of language to be included in the risk.

DR. JENSEN: Yes. Thank you very much for including that.

Is that an adequate response to your first question? That's all we have.

Moving on to the second question.

MR. WREH: I have a question, Dr. Jensen, if you don't mind. This is Elijah Wreh.

DR. JENSEN: Yes, Mr. Wreh, go right ahead.

MR. WREH: I just want to piggyback on Veverly Edwards' question on skin irritation and this is for the FDA. I know FDA is recommending the device be classified as Class I, I believe 510(k) exempt. My only question to the FDA folks is since this product would be called Class I 510(k) exempt, would the FDA require biocompatibility testing for this product since one of the risks is skin irritation, because for most products that require a 510(k), the FDA does require biocompatibility testing for those products. So I'm not sure if the FDA will require bio-testing for this Class I 510(k) exempt product.

Thank you, Elijah Wreh.

DR. JENSEN: So Dr. Keszler, the question is whether or not biomaterials testing of a device would -- is part of a general control or if that would require a special control.

DR. PINTO: This is Vivek Pinto, I can answer for Dr. Keszler, too.

So if the firm is using the same material and manufacturing methods on the subject device as a legally marketed predicate device, then I don't believe they would have to do additional biocompatibility testing. If one were to change the material, then -- you know, and that changed -- didn't, I guess, exceed the limitations for exemption, then that would be -- the company would have to do the testing and keep that on their records for future inspections in a postmarket.

DR. JENSEN: Okay, so that would be something that would be handled in a postmarket follow-up. Okay, thank you very much for that.

So our second question is, could you read that, please, Dr. Keszler?

DR. KESZLER: Section 513 of the Food, Drug, and Cosmetic Act states a device should be Class III if:

- insufficient information exists to determine that general controls are sufficient to provide reasonable assurance of its safety and effectiveness or that application of special controls would provide such assurance, AND
- if the device is life-supporting or life-sustaining, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury.

A device should be Class II if:

- general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness, AND
- there is sufficient information to establish special controls to provide such assurance.

A device should be Class I if:

- general controls are sufficient to provide reasonable assurance of the safety and effectiveness, OR

- insufficient information exists to:
  - determine that general controls are sufficient to provide reasonable assurance of the safety and effectiveness, OR
  - establish special controls to provide such assurance, BUT
    I. 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
    II. does not present a potential unreasonable risk of illness or injury.

FDA does not believe that special controls will be required for acupressure devices under product code "MVV" and that general controls will be sufficient to provide a reasonable assurance of the safety and effectiveness for acupressure devices. As such, FDA believes that Class I is the appropriate classification for acupressure devices under product code "MVV."

Please discuss whether you agree with FDA's proposed classification of Class I with general controls for acupressure devices under product code "MVV." If you do not agree with FDA's proposed classification, please provide your rationale for recommending a different classification.

DR. JENSEN: Thank you very much.

So I'd like to take this opportunity to go around to the panelists to see if they agree with the FDA's classification of a Class I.

Dr. Galen.

DR. GALEN: Yes.

DR. JENSEN: Dr. McDavitt.

DR. McDAVITT: Yes.

DR. JENSEN: Dr. Kennedy.

DR. KENNEDY: I do. Although I will note, I think the evidence is fairly weak.

DR. JENSEN: Dr. Ortiz-Aguayo.

DR. ORTIZ-AGUAYO: Yes.

DR. JENSEN: Dr. Dorsey.

DR. DORSEY: Yes.

DR. JENSEN: Dr. Lyden.

DR. LYDEN: I agree it's a Class I, not II or III, but I'd like to ask a question about Class 0 if I could.

DR. JENSEN: Go ahead.

DR. LYDEN: So I quickly went through the reference list provided by Dr. Keszler, and most of the publications were published prior to our modern adoption of standards of rigor including blinding and randomization and power analysis and some were published in journals that to this day don't follow those guidelines. And in the absence of a meta-analysis that includes an estimate of publication bias, I wonder if it's appropriate to postpone this decision because a Class I designation connotes an endorsement of efficacy despite all the fine print that says it doesn't. It does, and I wonder if it's a little premature to classify the device based on the literature that we have available. That's a question to FDA.

DR. JENSEN: And a very, very reasonable question because I think many of the panelists agree that the data may not be of the highest rigor for a device.

So Dr. Pinto, Dr. Keszler, can you please address Dr. Lyden's question?

DR. PINTO: Yeah. Thank you, Dr. Lyden.

So just to clarify, there's no Class 0 for devices and this is -- you know, these are preamendment devices so we're trying to determine which classification best fits. We do understand that these devices have been legally marketed over a long period of time and

we have our evidence where we're making our recommendation and we wouldn't -- at this point in time we're not making the final decision, we're trying to gather information, expand our network and hear from you. And then we're going to follow up with internal discussions and decisions. But if there's -- right now if there is insufficient information for a Class I and there's things you want us to really -- you know, you brought up points, but if you have other points for us to really consider, too, this is definitely the right time to bring up why Class II or III would be appropriate and the rationale we should use.

DR. LYDEN: Copy that. You know, if my only choice is I-II-III, I agree with I, but I would recommend the Agency complete a formal meta-analysis that really analyzes the quality of the data and if it's insufficient, consider a warning that -- an actual warning that there's insufficient information to support effectiveness of this device, you can wear it if you want to, but we're not saying it works.

DR. JENSEN: Thank you, Dr. Lyden.

Dr. Cooper.

DR. COOPER: Yeah, I agree. I mean, I can't see it being anything better than a Class I although it would be nice to see more scientific studies and more data to support it.

DR. JENSEN: Dr. Pilitsis.

DR. PILITSIS: I agree, it's a Class I. I think the risk is, in my view, pretty low. So I like Dr. Lyden's suggestion to say hey, we can't tell you if it works based on the evidence, but as a Class I.

DR. JENSEN: Dr. Johnston.

DR. JOHNSTON: I agree, Class I and for Dr. Lyden's comments, as well.

DR. JENSEN: So Dr. Pinto, with regard to this question, the Panel generally believes that the device belongs as a Class I. Having said that, that is really more in terms of safety as opposed to efficacy and that we feel that the data is lacking and that perhaps a more

deep dive of the data could either show certain indications, for example, like it doesn't work for post-chemotherapy nausea and it perhaps does work for pregnancy nausea, but that the data is lacking and that it may actually be appropriate to classify the device but say that the efficacy is not -- has not been proven. Does that answer your question?

DR. PINTO: Yeah, thank you. Thank you very much, everybody, and Dr. Jensen. And we'll certainly consider that, you know, considering the limitations we do have, as well, from a regulatory standpoint.

DR. JENSEN: And is there -- there's a third question, is there not? That's it?

MS. EDWARDS: Oh, this is Veverly, the Consumer Rep. May I say something?

DR. JENSEN: Yes, please.

MS. EDWARDS: Okay. So I was listening to you all and my concern is with it not being able to -- just saying that it's insufficient and you can't guarantee. As a consumer, I have a problem with putting something like that out for a consumer because everyone doesn't have your level of intelligence or education, so if you're going to put that out there to the public, I think I would probably think Class II with needing more information, we don't know whether there was a placebo group. I mean, we've already established that it's weak as far as the data. So I think, to me, that would be a danger to the consumer. That's just me. I mean, I could be wrong.

DR. JENSEN: Dr. Pinto or Dr. Keszler, do you have any comment upon what Ms. Edwards has said?

DR. PINTO: I don't have any specific comment. Again, we're trying to figure where's the right place to legally -- or to classify these devices that are already legally marketed right now. But we definitely hear your comment.

DR. JENSEN: I think, Ms. Edwards, and maybe I misunderstand all the classifications, but it seems to me that Class II would mean that there is special controls that help answer

the question that we're all discussing and I don't think that's necessarily the case because I don't think making the companies go back and do more testing somehow puts it -- you know, and doing trials puts it back into the Class II realm. But I think that if there's labeling saying that this product has not been shown to be -- and I think we all agree, the product is safe, I mean, you can put a band on your wrist and if you position it properly, you know you're not going to have danger to it, but it's really whether or not it works, is it actually efficacious, and I think that there may be a way and we've stated that to the FDA, that the consumer needs to know you may wear this product safely but we don't have evidence that shows that it actually works and I think that may be the best that we can do.

MS. EDWARDS: And so you think that -- oh, I'm sorry. So you think that --

DR. COOPER: Go ahead.

MS. EDWARDS: -- with just labeling and put it in a certain place that the consumer -- because you did -- I did hear some people concerned about where, you know, if it was placed at a certain point it could cause some other type of -- was it neurological issues or something else? So, I mean, that's just me as a consumer. I mean, I hear you, I could read the label and I probably could read it and know where to put it, but we're talking about the American public at large. You know, I could be wrong. It's just my concern.

DR. JENSEN: And I think it's a valid concern, but I guess we have to work within the framework that we have right now in terms of how we classify it and what we can say to the consumer.

DR. COOPER: The concern basically is --

DR. JENSEN: Sorry, just a moment. So Dr. Cooper and then Dr. Loftus.

Dr. Cooper.

DR. COOPER: I mean, I think the concern is that people are -- companies are likely to say it's FDA approved and that would give kind of a blessing. Consumers will view that

that's a blessing by the FDA or --

DR. JENSEN: Dr. Loftus and then we'll go to Mr. Wreh.

Dr. Loftus.

DR. LOFTUS: Yeah, thanks. I mean, I realize I'm not a panelist, but if you'll allow me the privilege of making a comment, and I think what you're saying are all very salient comments, all very appropriate. You're bumping up against the somewhat artificial nature of the exercise, right, I mean, we're here trying to determine a classification for devices that have been legally marketed for years, all these questions are appropriate. You know, I would suggest we don't want to go home with no classification or we'll be back, so it is -- there is an element of artificiality to it and obviously a whole group of very intelligent people have figured that out, but we are a little bit constrained in that way.

DR. JENSEN: Thank you very much for that comment.

Mr. Wreh.

MR. WREH: Yeah, I apologize. I know I'm not a voting member on this Panel, but I just want to comment, you know, I agree with the FDA assessment that the device should be called Class I 510(k) exempt. My only comment to the Agency is, you know, it can either clarify it would be best if it were used, you know, will it be OTC or prescription only and then secondarily, can the FDA also clarify how would they strengthen the device labeling since members of the Panel have concerns on the device product labeling. Thank you.

DR. JENSEN: Thank you very much for your comment.

So it's now 11:08 and we've been through the first two devices. I would suggest that we go ahead and break for lunch, come back at 12:00 and then resume looking at our third device for the day, is that acceptable to the panelists?

(No response.)

DR. JENSEN: Okay. Any comments before I log us off?

DR. LOFTUS: Just to ask a question and I guess I should know the answer, but one of the video guys, are we just going to leave this running all the way through lunch and come back or not log in again, hopefully?

DR. JENSEN: I will leave that to our video experts.

MR. VEIZIS: Yes, yes, please leave all your connections up. If you'd like, you can mute your video, do whatever, but we're going to basically take the webcast -- you know, we'll leave that going, we'll just put a graphic up for now.

DR. JENSEN: Wonderful.

DR. LOFTUS: Thank you very much.

DR. JENSEN: Thank you.

MR. VEIZIS: Thank you all.

DR. JENSEN: See you all at noon.

(Whereupon, at 11:09 a.m. a lunch recess was taken.)

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AFTERNOON SESSION

(12:01 p.m.)

DR. JENSEN: Okay. Welcome back, everybody. Hope you all had an opportunity to get some lunch. Hopefully, alkaline tide won't set in and we'll all fall asleep. The next device -- have some interesting conversation. So we're going to move on to our third device, which is the electro-acupuncture stimulator, and we will now hear from Dr. Robert Stefani. He will present on the electro-acupuncture stimulator.

Please proceed, Dr. Stefani.

DR. STEFANI: Hello, my name is Robert Stefani and I'm a lead reviewer in the Division of Neuromodulation and Physical Medicine Devices within the Office of Neurological and Physical Medicine Devices in CDRH's Office of Product Evaluation and Quality.

Today, I'll be talking about information regarding the effort to classify electro-acupuncture stimulators under product code BWK. These devices are currently unclassified and we are looking for your thoughts and recommendations on the appropriate regulatory classification for these devices.

Here is the outline for today's presentation. These are the items that will be discussed.

Electro-acupuncture stimulators are designed to function based on a principle of traditional Chinese medicine, that stimulation of certain areas of the body, in other words, acupuncture points, can have a physiological influence on non-adjacent body parts or organ systems. The device applies a low-voltage electric current to stimulate these acupuncture points via percutaneous or transcutaneous electrodes. Some devices also measure skin conductance to identify acupuncture points by their high conductivity or come with

accessory applicators intended to aid in placement of acupuncture needles.

Typical indications for use statements are provided here. These are representative of the indications for use statements for cleared electro-acupuncture stimulators. Broadly, these devices are indicated for use in the practice of acupuncture and for pain relief. Electro-acupuncture stimulators are indicated for prescription use.

Electro-acupuncture stimulators are a preamendments, unclassified device type. This means that this device type was marketed prior to the Medical Device Amendments Act of 1976. It was not classified by the original classification panels. Currently, these devices are being regulated through the 510(k) pathway and are cleared for marketing if their intended use and technological characteristics are substantially equivalent to a legally marketed predicate device. Since these devices are unclassified, there is no regulation associated with the BWK product code.

Although not shown in the Executive Summary, on May 14th, 2021 we conducted an updated search to identify the current total number of 510(k)-cleared electro-acupuncture stimulators. To date, there have been 21 electro-acupuncture stimulators cleared through the 510(k) pathway under the BWK product code, the first clearance occurring in 1979 and the last in 2020.

The vast majority of cleared electro-acupuncture stimulators are intended for general use in the practice of acupuncture and many are intended specifically for pain. Pain is a subjective sensation of discomfort caused by either actual or potential injury to the body that can be described in terms of location, intensity, duration, and nature.

The pathophysiology is complex, but can be generally described as painful stimuli arising in the periphery which are subsequently received by nociceptors that communicate peripheral nociceptive input to the dorsal horn of the spinal column where interneuron modulation occurs as the signals are distributed to other structures of the CNS and this

includes the brain stem, limbic system, and some somatosensory regions of the cortex. The transmission of pain and modulation of the signaling involve multiple widely distributed bidirectional pathways of excitatory and inhibitory receptors and neurotransmitters that serve as targets for pain treatment in the form of drugs and physical interventions.

Treatment and management of pain is complex and continues to evolve. The appropriate therapeutic strategy for the treatment of pain is dependent upon accurate evaluation of the cause of pain, as well as the type and chronicity of the pain condition. Whenever possible, a nociceptive or neuropathic source for the underlying cause of pain should be identified and targeted for treatment.

Chronic pain is best managed with collaborative, multidisciplinary support including primary care, psychology or other behavioral health specialists, physical therapy, use of appropriate physical modalities including interventional pain and complementary and alternative health therapies.

Involving patients and their care through education on the mechanisms that contribute to chronic pain can reduce fear and anxiety which hinder improvement. Overall, it is important for the team to set reasonable expectations for response in order to achieve successful chronic pain management.

Pharmacologic therapy can be considered for patients with inadequate analgesia despite nonpharmacologic therapies. The optimal choice of pharmacologic therapy depends on the type of chronic pain syndrome, and neuropathic pain should be distinguished from nociceptive pain since treatments differ.

The patient's medical status, for example, cardiovascular, hepatic, renal, and cognitive issues may also affect the choice of drug due to the potential for drug side effects, drug clearance, and drug-to-drug interactions.

Interventional therapy for chronic pain ranges from office space injections into

muscles or joints to neurodestructive or neuromodulatory procedures used to treat more widespread pain. These interventions can be used in conjunction with rehabilitation and appropriate pharmacotherapy.

We conducted a literature review to identify any published information between January 1st, 2010 and December 31st, 2020 regarding the safety and effectiveness of electro-acupuncture stimulators. The search yielded 2,953 initial literature references. After duplicate articles were removed between databases, a total of 2,582 articles remained. Following a review of the titles and abstracts, a total of 570 articles remained for full-text review. Of these, 105 articles were determined to be relevant to the safety and effectiveness of electro-acupuncture stimulators.

The 105 selected studies consisted of 73 randomized clinical trials, 13 meta-analyses, seven systematic literature reviews, seven prospective studies, and five case series or reports. I'll briefly summarize some of the main take-home points from these review articles.

Reported adverse events for electro-acupuncture or EA stimulation were sporadic across selected indications. Of the 28 studies reviewed for device safety, 17 reported on adverse events associated with EA stimulation use in the selected indications.

Safety outcomes reported in these studies include mild fainting, ecchymosis, mild hematoma, skin pallor, skin pigmentation, vertigo, nausea, vomiting, chest tightness, unconsciousness, and death. It should be noted that the only instances of deaths were reported in three patients treated for schizophrenia from a single case series, but this may be the result of insufficient patient protections.

The three most frequently reported AEs were mild exacerbation of chemotherapy induced nausea and vomiting, skin pallor, and skin pigmentation. Most articles did not include counts of AEs, so it is difficult to discern the true frequency of AEs caused by

electro-acupuncture. However, there does not seem to be a statistical difference between EA stimulation and manual acupuncture in regard to AE incidents based on the three randomized controlled trials comparing AE rates between treatment types.

Ninety-five of the 105 articles reported on device effectiveness for a wide variety of indications. The majority reported on EA stimulation effectiveness in treating musculoskeletal pain, that was 42 articles, or postoperative pain and analgesic reduction, that was 17 articles. The remaining articles reported on neuropathic pain, stroke, stroke rehabilitation, cerebral palsy, Parkinson's disease, cerebral infarction, carpal tunnel syndrome, fatigue, headache or migraine, fibromyalgia, and motion sickness. There was also evidence that EA stimulation treatment may be favorable for treating stroke.

Overall, the literature demonstrates that EA stimulation treatment seems to have a significant effect on musculoskeletal pain, postoperative pain, and analgesic reduction and neuropathic pain compared to sham and control groups. But still, it does not have a significant effect compared to manual acupuncture or alternative treatments.

In summary, more evidence is needed to determine whether the usage of EA stimulation is consistently associated with the AE events reported and whether there is strong evidence of EA stimulation effectiveness in musculoskeletal, postoperative, neuropathic pain, analgesic reduction, and stroke indications.

There is little published evidence, and additional studies are needed to draw conclusions about EA stimulation treatment for stroke rehabilitation, Parkinson's disease, acute cerebral infarction, carpal tunnel syndrome, fatigue, fibromyalgia, and headache. All of these indications require further study.

The next three slides provide background information for medical device reports, or MDRs. This information was summarized previously in the presentation for vapocoolant devices under product code MLY.

To further contribute to the benefit-risk assessment of electro-acupuncture stimulators, MDRs were reviewed. The Manufacturer and User Facility Device Experience, or MAUDE, was reviewed for the device recall database. This information was summarized previously in the presentation for vapocoolant devices under product code MLY.

Our review of the recall database found no recalls for devices under the BWK product code.

To determine the appropriate classification for electro-acupuncture stimulators, we have identified risks associated with these devices and possible mitigations for these risks. We will be asking the Panel for input on the listed risks and mitigations.

To identify the risks of these devices, we used FDA's MAUDE database to identify MDRs and the information available to FDA regarding cleared devices. We also conducted the previously discussed literature review.

Here are the four risk categories we've identified for electro-acupuncture stimulators:

Number 1, adverse tissue reaction. This can result from improper cleaning of reusable patient-contacting components or non-biocompatible materials.

Number 2 is infection. This can result from non-sterile or contaminated needles and other types of electrodes that enter the epidermis or deeper layers of skin.

Number 3 is patient injury or discomfort, including electrical shock, burn, or bleeding. This can result from overstimulation or excessive trauma caused by percutaneous components.

And fourth, use error. This can result from inadequate instructions for use labeling.

We propose that special controls, in addition to general controls, can be established to mitigate the risks to health identified and provide a reasonable assurance of the safety and effectiveness of electro-acupuncture stimulators.

This is a risk/mitigation table which outlines the identified risks to health for this device type and the recommended controls to mitigate the identified risks.

To mitigate the risk of adverse tissue reaction, we recommend biocompatibility evaluation and labeling controls.

To mitigate the risk of infection, we recommend sterilization and cleaning validation, shelf-life testing, and labeling controls.

To mitigate the risk of patient injury or discomfort, we recommend electrical, mechanical, and thermal safety testing, electromagnetic compatibility testing, nonclinical performance testing, software validation, verification, and hazard analysis and labeling controls.

And fourth, to mitigate the risk of user error, we recommend labeling special controls.

Here's our proposed classification regulation for electro-acupuncture stimulators. Part (a) of the regulation defines the device as follows: An electro-acupuncture stimulator is a prescription device intended for medical purposes, such as pain relief, that is used to apply an electrical current to acupuncture points through electrodes in the practice of acupuncture by a qualified practitioner of acupuncture therapy. Furthermore, we are proposing these devices be classified as Class II devices with special controls.

The proposed special controls for this device are:

Number 1, the patient-contacting components of the device must be demonstrated to be biocompatible.

Second, performance testing must demonstrate the sterility of device components that are provided sterile.

Third, performance testing must demonstrate continued sterility, package integrity, and device functionality over the labeled shelf life for device components provided sterile.

Fourth, performance testing must validate cleaning procedures and demonstrate continued device functionality over the labeled shelf life for reusable patient-contacting components.

Fifth, performance testing must demonstrate electromagnetic compatibility and electrical, mechanical, and thermal safety in the intended use environment.

Continuing to Number 6, nonclinical performance testing of the device and electrodes must be conducted to validate the specified electrical output and duration of stimulation of the device.

Seven, software verification, validation, and hazard analysis must be performed.

Eight, labeling must include the following:

- Instructions for use, including identification and placement of appropriate electrodes, and the typical sensations experienced during treatment;
- Labeling should also include a warning stating that the device is only for use on clean, intact skin;
- A detailed summary of the electrical output and the device technical parameters;
- A shelf life for the applicators and components provided sterile;
- A statement that sterile components are intended for single use only; and
- Instructions on care and cleaning of the device for reusable components.

This concludes our presentation. Thank you so much for your time and attention and your thoughtful feedback on the following Panel questions.

DR. JENSEN: Thank you very much, Dr. Stefani, for your presentation.

I want to open the floor to the experts around the table to begin deliberating on electro-acupuncture stimulator devices, considering everything you have heard and read in your panel packs and heard in today's Open Public Hearing and from the presentations. Would anybody like to start?

Yes, Dr. Ortiz-Aguayo.

DR. ORTIZ-AGUAYO: I'm just wondering if we could get a little bit more information around the causation of the four deaths that were mentioned in the presentation.

DR. STEFANI: Sure, I'd be happy to provide a little bit more information. This was actually a case report published in 1981 and the cases were in China, I believe. So this was a case where these three patients -- you know, there's very limited information, I think we detailed this in the Executive Summary, there's very limited information in this case summary about patient protections and there was -- you know, they did hint to the fact that the device was not actually used as intended, that the -- basically, that the patients were not properly monitored throughout the course of this case series. So I would point out again that this was the only case where something like this was reported and there's a large amount of literature on the subject, but we still thought it was important to include in the Executive Summary.

DR. ORTIZ-AGUAYO: My apologies, I guess what I'm trying to get to there, if the authors mean that there was a causation relationship with the device or these were -- the deaths were associated to the devices.

DR. STEFANI: I believe that they were due -- that they were due to puncturing organs, so this was related to the use of the needles rather than the electrical stimulation. But you know, we're really -- you know, it's really not that clear, but they did say that it was due to perforation of internal organs. I think in one case it was the heart and the other might have been something in the neck that was punctured.

DR. ORTIZ-AGUAYO: Thank you.

DR. JENSEN: So I have a question. You know, we started out by saying this device is being used for pain control but then there were other uses that were included and of course, the one that caught my eye was stroke. I'm sure, Dr. Johnston, that probably

caught your eye, too. And so there wasn't anything in the summary that talked about it being pain in stroke patients but actually as improvement in Barthel index and NIH stroke score, which is -- I mean, that's a completely different issue when you're talking about stroke and you're talking about pain.

In addition, they also had the category of acute ischemic stroke, but they had a separate category of acute cerebral infarction, which is the same thing, and so I wasn't really certain why that was sort of called out and not included, and I think it was four cases of stroke.

But do you have any more information on these stroke patients, because my concern is that again, when we start talking about labeling or we start talking about indications, I would really hate for this device to get out there as a treatment for stroke when there is really no data to support that. So any comment about stroke or any of the other indications that weren't pain indications, because the literature was just not very strong on any of them, like Parkinson's and etc.

DR. PINTO: Hi. Oh, go ahead, Rob. You can go first.

DR. STEFANI: Sure. Yeah, that's a great point and I would just point out that of all the cleared devices, none of the currently cleared electro-acupuncture devices are indicated for stroke. The vast majority, as I mentioned, are just for general use during acupuncture therapy.

DR. JENSEN: Okay.

DR. STEFANI: And also, there were some directly indicated for pain. So I guess that's just what I would point out.

Vivek, I'm not sure if you had something else to add.

DR. PINTO: Yeah, that's what I was saying, they weren't cleared for this use, but we did want to make sure that we let you know of what we found in the literature that was --

you know, that we did end up reviewing after the systematic literature review, so there were other uses.

DR. JENSEN: Okay, so this is just pain that we're talking about here. Indications.

DR. PINTO: Well, they -- I'm not actually sure about that. You know, you bring up a good point, but the scales that were used for that aren't pain scales.

DR. JENSEN: Um-hum.

DR. PINTO: So it could be that they were also using it for other treatments in off-label use. So I don't have that specific information, but I do see the confusion.

DR. JENSEN: And one other point I have to make is that I noticed in the Executive Summary they talked about the device could be used as sort of this one contained device, everything that's used is provided by the manufacturer but it could also be used with other acupuncture needles. Right. So you could have acupuncture -- my reading of it was you could use acupuncture needles of your own, but the device would still work, right, you didn't have to use the acupuncture needles that come with the kit and if that's true, then there's a sterility issue there.

To me, if it's one product, then everything that's going to be used on that patient's skin, whether it's percutaneous or intradermal or subcutaneous, should all be in that one device. You shouldn't be able to use your needles from some other place because you can't guarantee sterility in that particular situation.

DR. STEFANI: I agree completely. So there's a wide variety of technological characteristics to these different devices, so the wording of that I can clarify a little bit. You know, I am not aware of any devices that are provided with -- that come with their own needles and then they allow other types of electrodes to be used. It's really on a case-by-case basis and that's why we included in the proposed special controls that it really -- the manufacturer really needs to identify the proper, you know, the correct

-- which electrodes should be used with the device. Some come with their own and can only be used with that specific electrode; others are indicated for use with 510(k)-cleared acupuncture needles, generally. So I think our thinking is that that would be covered with the labeling special controls.

DR. JENSEN: Okay.

DR. STEFANI: But that's certainly something to consider, yeah.

DR. JENSEN: Thank you.

So Dr. McDavitt and then, I think, Dr. Dorsey.

Dr. McDavitt, you can go first.

DR. McDAVITT: Thanks. So these devices aren't just used for acupuncture.

DR. JENSEN: Well, you muted yourself. There we go. You're muted again.

DR. McDAVITT: Okay, hold on a second.

(Pause.)

DR. McDAVITT: Sorry. So these devices are used for myofascial trigger points, as well, and so I'm not sure, are we just -- are we rating this only on acupuncture, because these are used interchangeably, so are we -- I sort of look at this like manipulation, it sounds like everybody but sometimes it's only called chiropractic. So are we considering, in this examination of this device, that we're treating everything beyond just acupuncture points or are we also considering myofascial treatment points?

DR. STEFANI: I think we're only considering acupuncture points under this regulation. So any other usage of the device would --

DR. McDAVITT: The reason I ask that is because they make sense if you overlap, if you look at the literature, so it's hard to tell. And so one of the things that pops in my mind about your issue of the organs is that acupuncture needles come textured and un-textured and when you use these devices with these stimulators and you're doing an acupuncture-

type stimulation, there's actually muscle contraction that goes on and when you use a textured needle, they walk. So you might see a needle on the tissue start at 2 inches of showing the needle and you come back and it's now showing an inch because as the muscle twitches it pulls the needle inward. So some of the -- whether the myofascial trigger points or the acupuncture sites, if they're inside muscle tissue, my concern would be that beyond the current density issues that you've already described, that in fact whether you use textured needles or not, they need to be checked as the device is on. I've been thinking things like a back muscle or something, you know, the lung tissue doesn't sit very far away from there and the backdrop of the actual needle becomes an important consideration.

DR. STEFANI: No, I agree, that's definitely important. Do you have a recommendation for an additional special control that might address that point?

DR. McDAVITT: I think that in terms of clinical practice, whether it be a myofascial trigger point, any type of tissue where the needle is in, I think that it should be recognized whether the needle is textured or not and that if it's being provided at the level of muscle contraction, the backdrop, there should be some clinical controls for the clinician to understand (a) what's the backdrop tissue, is it a textured needle or not, and that they're going to keep an eye on that, they're not just going to walk away and leave it because today there is a lot of -- that I'm aware of, there's a lot of people that are now trying to use multiple needles, multiple locations, and deeper levels of penetration using low-frequency stimulation, all of those would set up those risks.

DR. JENSEN: Thank you very much.

Let's see, I think Dr. Dorsey and then Dr. Cooper.

DR. DORSEY: There are people ahead of me, I'll come back later.

DR. JENSEN: Okay, Dr. Cooper.

DR. COOPER: Thank you. The only thing that I thought about was we should also

look at microshock hazard, if you're going to pierce the skin and do stimulation, then there is a risk of a microshock. And that could be done in fairly long stimulation. So maybe looking at things like optical isolation or batteries that prevent a current over a certain level, but at least it should be something -- it should be in the application.

DR. JENSEN: Great. Thank you very much.

Dr. Dorsey and Dr. Johnston.

DR. DORSEY: Dr. Johnston's ahead of me.

DR. JENSEN: Oh, she is. Okay, Dr. Johnston.

DR. JOHNSTON: I wanted to add to the comment that was previously made by Dr. McDavitt, that I was concerned about the three deaths, and I understand that there is not a lot of information about the three deaths, but I don't feel like we can dismiss them. So I would be in favor of some kind of special control that addresses what we think may be happening with those two deaths and based on what we just heard -- that a special control could be some kind of labeling that would indicate that if the needles are used in any tissue or textured or whatever qualifications you want to say, that it can result in death. I think that needs to be part of the labeling.

DR. JENSEN: Great, thank you.

Okay, Dr. Dorsey.

DR. DORSEY: I think Dr. Kennedy, then I'll go.

DR. KENNEDY: He's just being a gentleman to us all. So I'll just point out, and I don't want to rehash because we did this on our last discussion, but I do think this is very similar where we're dealing with a device that has been out for a while, but yet the quality of evidence is exceedingly low. Most of the studies report statistical but not clinically meaningful differences, most of them suffer from poor controls or strong bias. The overall body of evidence is exceedingly low for therapeutic effects of pain from these devices. I

just want to put that on the record.

DR. JENSEN: Thank you.

Dr. Dorsey.

DR. DORSEY: I agree with Dr. Kennedy. I'd probably go further, I think there's reasonable assurance of lack of efficacy or lack of effectiveness of these devices.

DR. KENNEDY: I'll echo that.

DR. DORSEY: I see no reason why these devices should be on the market and I think given the significant safety effects, that they shouldn't be.

DR. JENSEN: Okay, thank you.

Anybody else have any comments?

(No response.)

DR. JENSEN: No? Have we adequately discussed this, these issues that have been brought forth?

(No response.)

DR. JENSEN: I don't see anybody else raising their hand, so I think it's time to focus on the discussion of the questions. So at this time let's focus our discussion on the FDA questions, and copies of the questions can be found in your electronic documents and on the FDA website. Dr. Robert Stafani will now read FDA Question Number 1, there are three in total.

Dr. Stafani, please proceed.

DR. STEFANI: Sorry about that, I was muted. Can you let me know if you can see the shared screen all right?

DR. JENSEN: Um-hum. Yes.

DR. STEFANI: Thank you. So FDA has identified the following risks to health for electro-acupuncture stimulators:

- Adverse tissue reaction
- Infection
- Patient injury or discomfort including electrical shock or burn and bleeding
- User error

Our question to the Panel is whether you would please comment on whether you agree with inclusion of all the risks in the overall risk assessment of electro-acupuncture stimulators under product code "BWK." In addition, please comment on whether you believe that any additional risks should be included in the overall risk assessment of these electro-acupuncture stimulators.

AUTOMATED RECORDING: Recording stopped. Recording in progress.

DR. JENSEN: So can we get back to the overall Panel picture, please? So I think that we have addressed some more risks in addition to the ones that you haven't included in the overall risk assessment. I'll just paraphrase what my colleagues have said.

One is that the device should be packaged with all components that are for use for sterility reasons, they should be packaged and marketed only for acupuncture and not for anything else, like myofascial use, trigger-point use, and that it's very important that there's the recommendation that the location of the needle needs to remain in the cutaneous, subcutaneous region, not in the muscle, that is placed into the muscle and is being used for some sort of myofascial trigger point relief; that the operator needs to recognize that the type of needle that's used, i.e., textured versus non-textured needle, may move in the muscle and migrate into -- deeper into the muscle or into another organ and so placement is of paramount importance.

There needs to be -- shock hazards need to be considered and there should be some controls put into place, such as batteries that limit the microshock hazards, such as batteries that can limit the amount of current; that labeling should include that if the device

is not used in the approved locations, i.e., use in organs, that can lead to death. So these are things that should be included in the risks.

Panel members, anybody else have anything else to add?

(No response.)

DR. JENSEN: So that would be the answer to Question Number 1, I believe.

DR. STEFANI: Great. Thank you so much, it's really fantastic feedback. It will certainly give us a lot to consider when we go back over this. So thank you for that.

DR. JENSEN: Um-hum. You're welcome. So let's go to Question 2.

DR. STEFANI: All right, Question 2. Section 513 of the Food, Drug, and Cosmetic Act states a device should be Class III if:

- insufficient information exists to determine that general controls are sufficient to provide reasonable assurance of its safety and effectiveness or 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 if the device presents a potential unreasonable risk of illness or injury.

A device should be Class II if:

- general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness, AND
- there is sufficient information to establish special controls to provide such assurance.

A device should be Class I if:

- general controls are sufficient to provide reasonable assurance of the safety and effectiveness, OR
- insufficient information exists to:

- determine that general controls are sufficient to provide reasonable assurance of the safety and effectiveness, OR
- establish special controls to provide such assurance, BUT
  - I. 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
  - II. does not present a potential unreasonable risk of illness or injury.

FDA believes general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness and sufficient information exists to establish special controls to adequately mitigate the risks to health and provide reasonable assurance of device safety and effectiveness for this device type. As such, FDA believes that Class II is the appropriate classification for electro-acupuncture stimulators. Following is a risk/mitigation table which outlines the identified risks to health for this device type and the recommended controls to mitigate the identified risks.

To mitigate the risk of adverse tissue reaction, we recommend biocompatibility evaluation and labeling controls.

To mitigate the risk of infection, we recommend sterilization and cleaning validation, shelf-life testing, and labeling controls.

To mitigate the risk of patient injury or discomfort, we recommend electrical, mechanical, and thermal safety testing, electromagnetic compatibility testing, nonclinical performance testing, software validation, verification, and hazard analysis, and labeling controls.

And lastly, to mitigate the risk of user error, we recommend labeling special controls.

We ask that you please discuss whether the identified special controls for electro-acupuncture stimulators appropriately mitigate the identified risks to health and whether

additional or different special controls are recommended. These are the first six proposed special controls. So the first is:

1. The patient-contacting components of the device must be demonstrated to be biocompatible.
2. Performance testing must demonstrate the sterility of device components that are provided sterile.
3. Performance testing must demonstrate continued sterility, package integrity, and device functionality over the labeled shelf life for device components provided sterile.
4. Performance testing must validate cleaning procedures and demonstrate continued device functionality over the labeled shelf life for reusable patient-contacting components.
5. Performance testing must demonstrate electromagnetic compatibility and electrical, mechanical, and thermal safety in the intended use environment.
6. Nonclinical performance testing of the device and electrodes must be conducted to validate the specified electrical output and duration of stimulation of the device.

And these are the remaining special controls:

7. Software verification, validation, and hazard analysis must be performed.
8. Labeling must include the following:
    a. Instructions for use, including identification and placement of appropriate electrodes, and the typical sensations experienced during treatment;
    b. Also a warning stating that the device is only for use on clean, intact skin;
    c. Also detailed summary of the electrical output and the device technical parameters;

d. A shelf life for the applicators and components provided sterile;

e. A statement that sterile components are intended for single use only; and finally

f. Instructions on care and cleaning of the device for reusable components.

And we ask you to please discuss whether the identified special controls for electro-acupuncture stimulators appropriately mitigate the identified risks to health and whether additional or different special controls are needed.

DR. JENSEN: Okay. Could you please put back up the pictures of the entire Panel again? Sorry, not the discussion but the people, so I can see who's --

DR. STEFANI: Oh.

DR. JENSEN: Yeah.

DR. STEFANI: I'm not sure how to -- should I just stop sharing?

DR. JENSEN: Yeah, why don't you stop sharing for a moment? That would be great.

DR. STEFANI: All right.

DR. JENSEN: There we go, thank you.

Okay, so to our Panel members, I think in looking at the list of recommendations, it covers everything that at least we discussed that we were concerned about in terms of use of the device and the sterility, etc. Does anybody have anything else that they want to add to that list?

Dr. McDavitt.

DR. McDAVITT: Yeah, I tried to raise my hand during the first discussion but because we were off screen, I guess nobody saw that. I just wanted to clarify, are we saying that we're coming at it and saying this is not to be used on myofascial or are we just addressing this as acupuncture?

DR. STEFANI: We're addressing this as acupuncture.

DR. McDAVITT: Okay, because I heard in the -- I think I heard it from Dr. Jensen, I thought I understood that you were also saying that it should not be used and I wasn't comfortable with saying that because we were just talking about acupuncture.

The last thing that I wanted to ask about is I think there was a comment also made about everything in the box being sterile and if we look at people who are providing acupuncture and dry needling today, they pull a sterile needle out of the case and they use a gloved hand where the glove isn't sterile. And so are we now saying that -- if we're saying that everything has to be sterile, is that really an unnecessary statement or inappropriate statement when, in fact, the technique by itself isn't necessarily sterile?

I mean, by application, CDC says to alcohol wipe non-sterile glove with sterile needle as long as you're not touching the needle and now we're saying that you can do the same technique, stick the needle in and you clip on an electrode that has been sterilized, that that's not an appropriate technique if, in fact, you're saying the whole thing has to be in the box. So I just wanted to be clear on that. Am I being more confusing?

DR. JENSEN: No, I think my comment was that I read somewhere in the summary that the device can also be used with other needles that don't come in the pack, which is fine except that if you're expecting the entire device to conform to sterility, then you may want to say listen, the device needs to be used with all of the components instead of leaving it up to the user to pick and choose other acupuncture needles. Now, maybe that's -- I don't do acupuncture --

DR. McDAVITT: Yeah.

DR. JENSEN: -- so I really don't know if that's appropriate or not, but I was trying to make sure the entire system was sterile from stem to stern.

DR. McDAVITT: Well, in clinical practice and CDC guidelines that you're instructed in handling dry needling or acupuncture needles, it doesn't require a sterile glove, it just

requires a sterile needle.

DR. JENSEN: Right.

DR. McDAVITT: And the skin prep is only alcohol. So if, in fact, the same technique is used, so if I pull out an e-stim 130 that is on this list and I do an acupuncture needle into a trigger point or acupuncture site, so I'm doing the same technique that's acceptable, and now I clip the electrodes on, there's no difference in the sterility area of problem. So I was just saying that in clinical practice nobody gets a box, what they do is they get the stimulator and they get sterile needles that are dated for a duration, they peel the sterile needle open, stick the needle in and clip the electrode to it and that's how it's done conventionally. And so I just was trying to be clear that I was understanding and you weren't saying everything had to be sterile because that's not how it's done.

DR. JENSEN: Right, we're not -- I wasn't implying that the procedure is done sterilized --

DR. McDAVITT: Okay.

DR. JENSEN: -- in all the components.

DR. McDAVITT: Okay, thank you. That clarifies it. Sorry to drag us through that, but I just wanted to be clear.

DR. JENSEN: No, that's --

(Cross-talk.)

DR. STEFANI: -- one more detail, if you don't mind.

DR. JENSEN: Go ahead.

DR. STEFANI: I would also point out that not all of these devices have percutaneous components. Some of them are just providing cutaneous electrodes --

DR. JENSEN: Sure.

DR. STEFANI: -- you know, like -- that may be used for something like a TENS device

for transcutaneous neurostimulation. So these are not -- these are not provided sterile, typically. Yeah.

DR. McDAVITT: Correct. The overall treatment, though, is by electronic parameters, it's a certain phase duration, intensity and frequency. It could be percutaneous or subcutaneous, I get that part.

DR. STEFANI: Sure. I'm just talking about the sterility aspects, so yeah, it would come with cutaneous electrodes, potentially, that were not sterile.

DR. JENSEN: Okay. Dr. Ortiz-Aguayo.

DR. ORTIZ-AGUAYO: I was just wondering if one way to address this is to ensure that the device makers list what are compatible end-user devices, right, whether those are needles or electrodes, etc., to try to reduce that potential risk.

DR. PINTO: That's what we would look for in the substantial equivalence review, too.

DR. JENSEN: Okay, thank you.

Dr. Galen, did you have something you wanted to add? No?

DR. GALEN: Sorry, I was muted. No, I do not have anything to add. Sorry.

DR. JENSEN: Okay. Anybody else have anything to add?

Yes, Dr. Loftus.

(Audio feedback.)

DR. JENSEN: Oh, I think you're getting feedback, we're not hearing you right. You sound like you're under water.

(Audio feedback.)

DR. JENSEN: No, you're echoing, it's bad echo.

(Audio feedback.)

MR. VEIZIS: Yeah, Dr. Loftus, you can jump off and just come right back in, that

should take care of it. Okay, okay.

DR. JENSEN: Okay. All right, anybody else have anything to say?

(No response.)

DR. JENSEN: Okay, so can you put Question 2 back up?

DR. STEFANI: Okay, sure.

(Pause.)

DR. STEFANI: All right, Question 2 is back up. Should I move forward --

DR. JENSEN: No, I'm just looking at it again. I think that in response to Question 2, we agree with all of the -- all the bullet points that you have there, having to do with the special controls, I don't think we had any other special controls to include. One thing to include would be to list the compatibility of the devices with other items, but otherwise I think we've answered Question 2.

DR. STEFANI: Okay. Would you say that 8a, that special control labeling must include the following instructions for use including identification and placement of appropriate electrodes, do you think that would be sufficient?

DR. JENSEN: As we discussed earlier, we think there needs to be perhaps more clarification --

DR. STEFANI: Okay.

DR. JENSEN: -- about that appropriate placement of the electrodes, meaning it needs to be avoided, they're being placed into muscle or organs, at least a warning to that because of what could potentially happen based upon the previous discussion.

DR. STEFANI: Understood, thank you.

DR. JOHNSTON: If I could make a comment, Dr. Jensen.

DR. JENSEN: Is that Dr. Johnston?

DR. JOHNSTON: Yes.

DR. JENSEN: Yes, please, go ahead and make a comment.

DR. JOHNSTON: Okay, just that the labeling indicate that erroneous use may result in death, I don't believe that that's in there.

DR. JENSEN: Yes, thank you for bringing that back up. Yes, as Dr. Johnston has said, one of the potential adverse events that can happen with inappropriate use of the device is death. And organ injury. Shall we go on?

DR. STEFANI: Sure.

DR. JENSEN: That was my comment, does 8a cover placement of electrodes, myofascial, 8a? Yes. So this device is being approved for acupuncture, correct?

DR. STEFANI: Yes.

DR. JENSEN: It's not being approved, not that you can't use it off label, but it's not being approved for myofascial treatments? This is not --

DR. STEFANI: So as of now, we're not calling out myofascial treatments in any way, so I can back up to the identification that I read there in Question 1. Sorry about this, I'm kind of going wild here scrolling through.

So going back to the identification, so we're saying an electro-acupuncture stimulator is a prescription device intended for medical purposes, such as pain relief, that is used to apply an electrical current to acupuncture points through electrodes in the practice of acupuncture by a qualified practitioner of acupuncture therapy.

DR. JENSEN: Okay.

DR. STEFANI: So our intent is this is being indicated for use during acupuncture therapy.

DR. JENSEN: All right. Therefore if someone chooses to use it for myofascial pain therapy, that is an off-label use.

Am I correct, Dr. McDavitt?

DR. McDAVITT: Sounds like that, yes.

DR. JENSEN: Thank you.

So let's go on to Question 3.

DR. STEFANI: Okay, thank you. So our third question, we ask you to please discuss whether you agree with FDA's proposed classification of Class II with special controls for electro-acupuncture stimulators under product code "BWK." If you do not agree with FDA's proposed classification, please provide your rationale for recommending a different classification.

DR. JENSEN: Okay, if you could stop sharing your screen so I can see the panelists again, so I can see the panelists.

All right, so Dr. Lyden.

DR. LYDEN: I'm sensitive to the comment made earlier about sufficient evidence of lack of efficacy. If there's sufficient evidence of lack of efficacy, then how do we believe that the risks are outweighed by a clinical benefit?

DR. JENSEN: So you are choosing to ask the question and not agree or disagree to the classification of Class II?

DR. LYDEN: Yeah.

DR. JENSEN: Okay. Dr. Galen.

DR. GALEN: I would like to echo Dr. Lyden's comments, as well, and I agree with that classification but I think the evidence needs to be noted.

DR. JENSEN: Dr. Pilitsis.

DR. PILITSIS: I agree with Class II and I would just note the evidence.

DR. JENSEN: Thank you. Dr. Ortiz -- I'm getting to you, Dr. Johnston.

Dr. Ortiz-Aguayo.

DR. ORTIZ-AGUAYO: Agree with Class II with the note of efficacy.

DR. JENSEN: Dr. Johnston.

DR. JOHNSTON: I was going to ask a question. In Class III there is the note that unreasonable risk of illness or injury is a reason to go to Class III, so my question was if there is lack of efficacy and effectiveness data and there is risk identified, can that be considered in the realm of Class III because it is unreasonable risk?

DR. JENSEN: Right. So I was thinking the same thing except that it was a Class III, which is what you just said, and then there's the "and" and the "and" part has to do with it being life-threatening or life-sustaining, is that correct? To our FDA Panel, am I remembering that correctly?

DR. DORSEY: No, I don't think that's right. I agree with Dr. Johnston, it says if the device -- so it's the "and" in addition to being life-supporting and life-sustaining, that's fine, but there's an "or" if the device presents a potential unreasonable risk of illness or injury. So I agree that if the devices have to remain on the market, that it should be Class III because (1) there's insufficient information existing to determine that general controls are sufficient to provide reasonable assurance of safety and effectiveness, and the device presents a potential unreasonable risk of injury or illness.

DR. JENSEN: Can you please put back up the definition of Class III just so we can all see it again?

DR. PINTO: Could I also invite Sergio or Megha to comment on the classification, too? I guess at the appropriate time. Would that be okay, Dr. Jensen?

DR. JENSEN: Yes, that would be fine. I'm sorry.

DR. PINTO: Yeah, I mean, as Rob is already showing on the screen, the criteria for Class III are listed here on the slide and we're accurately summarizing it, Dr. Dorsey.

DR. JOHNSTON: So Dr. Jensen, to answer your question, if that's the case, then I would not agree that it's Class II and would argue it's Class III based on that information.

DR. JENSEN: So my question to you, Dr. Johnston, and this is not a challenge, it's just for discussion, what points do we consider a potential unreasonable risk of illness or injury? We have discussed several potential risks that didn't seem to be borne out in the literature with the exception of the four deaths and there was -- I think there was a seizure and there was one other thing.

So to the Panel, what is the criteria or the threshold for potential unreasonable risk of illness or injury with this device, if in the majority of cases there has not been significant adverse events that reached the level of life-threatening?

DR. LYDEN: I think the argument is it was asserted that there's sufficient evidence that the procedure is not efficacious. So in the face of zero benefit, an infinitesimal amount of risk outweighs the equation because there's no benefit.

DR. JENSEN: Um-hum.

DR. LYDEN: So you could have, you know, pain and discomfort as your risk, we've got more than that, but if all you had was pain and discomfort in the face of zero benefit, the scale tips against the device.

DR. JENSEN: Um-hum. So can we go back to the entire Panel, stop sharing the screen for a minute? There we go. So I think that's a very reasonable argument and I'd like to hear from some of the other panelists, too.

Dr. Kennedy, how do you feel about this?

DR. KENNEDY: Yeah, I was one of the people that argued that the evidence was pretty poor for it and I think it was very well articulated that the evidence for it or more likely, the preponderance of evidence showing it doesn't work is pretty strong, therefore risk-to-benefit ratio starts to change in favor of this not having a favorable outcome. Even if there's a minority risk, there still is a level of risk. We do have reports of death in the literature, I mean, that's different than a lot of other things we have, although I think that's

pretty minor, but I would be in favor of Class III.

DR. JENSEN: Dr. Cooper.

DR. COOPER: Yeah, I think this is tough because they've been on the market, they've been approved, but I actually would lean towards making them a Class III, which would actually essentially push manufacturers to gather the evidence in order to demonstrate greater safety and efficacy and then we could -- not we, but the FDA could revisit this at some time in the future.

DR. JENSEN: Dr. McDavitt.

DR. McDAVITT: Can someone explain to me what the outcome -- well, obvious with this company, if it's practical it's put into a Class III, what actually the -- what actually happens?

DR. JENSEN: So Dr. Stefani or Dr. Pinto, can you enlighten us?

DR. PINTO: Yeah, I actually invite Sergio back, if he can respond to that. You know, this is a recommendation right now, so we have to see what, if any, outcomes would be for cleared devices already and those manufacturers.

But Sergio, do you have any response?

MR. DE DEL CASTILLO: Sure. So as Megha summarized earlier today, we'll take all the recommendations from the Panel today, including whether or not that we should say this is a Class III type device. We will then go over the proposed rule in the *Federal Register*, which would announce whatever FDA determines to be the appropriate classification. If we hypothetically do say it should be Class III, we'll gather comments from the public about that and then, based on our review of those comments, then we'll then go out with a final rule on the final classification. If that is Class III, what that means is that all the devices that are currently legally marketed would have to come in with a PMA and sufficient evidence to demonstrate a reasonable assurance of safety and effectiveness.

DR. JENSEN: Thank you.

So I'm going back to Dr. Ortiz-Aguayo. Based upon the conversation that we had, do you want to comment again?

DR. ORTIZ-AGUAYO: Yes. I think it's a compelling argument to make it a Class III.

DR. JENSEN: Dr. Pilitsis.

DR. PILITSIS: I'm going to be the outlier here. You know, so I treat a number of patients with chronic pain, that probably makes up 70% of my practice, and when we do a lot of randomized controlled trials or studies, because there is not a good phenotype we often end up with results similar to this and it's something that's plagued the field for things that are much more invasive than this device is, for instance, deep brain stimulation, but I do that in a subset of patients that I think will do well with it.

And so I think the issue here, in terms of my interpretation of what was said, so maybe I'm off, but we had the four deaths, which is the major issue, and those we don't have a lot of detail on, they were 30 years ago, they were in a place where there's some differences in how data is collected, and I don't know, but I bet that some things weren't being used appropriately.

And I do think it is dicey in any neuromodulation device to say hey, we can use this with whatever off-the-shelf needles and I'm not sure that that's okay because that's not -- we never do that with anything else. So I would remain at a Class II using the device with how it's packaged and not saying hey, you can augment this with anything else, because I bet that's when people get --

DR. JENSEN: Okay, thank you.

Dr. Galen.

DR. GALEN: Yes, I'm still kind of lost on the definition of it. I was reading through my manual that I printed and what I do not see is definitely the evidence side of it, that's

definitely concerning, there needs to be more evidence on the effectiveness of it. But at the same time, in terms of this, yes, there are risks and there are some mitigations that have been recommended, I would still kind of lean towards Class II rather than a Class III at this point.

DR. JENSEN: Okay. And Dr. Lyden, back around to you.

DR. LYDEN: Class III.

DR. JENSEN: All right. So Dr. Pinto, Dr. Stefani, in summary, there has been robust discussion over whether or not this should be a Class II versus a Class III device. The major concern is the lack of evidence for efficacy for really any of the indications, not only just pain, for other indications, too, like stroke, etc., and a concern that's not only with the some of the risks that you have identified, other risks that have come up, particularly around having to do with inappropriate placement of the device.

And Dr. Loftus is waving his hand at me. No?

(Audio feedback.)

DR. JENSEN: Still can't hear you.

(Audio feedback.)

DR. JENSEN: Okay. So at this point in time, in answer to the question of whether or not we agree with the FDA making this a Class II, the Panel is split on actually making it -- between making it -- leaving it as a Class II and making it a Class III secondary to the fact that there have been some serious adverse events that have been reported, albeit without very good understanding of the nature of why those serious events occurred, i.e., the deaths. And so at this point in time we cannot give you a recommendation for one class or the other and feel that there needs to be more investigation. Does that help?

DR. PINTO: Yeah. Thank you, panelists, and -- sorry, Dr. Jensen, it does help a lot. You know --

DR. JENSEN: Sorry.

DR. PINTO: I think maybe someone -- you know, this is a challenging one. You know, we didn't receive any events in such a long time in our surveillance system for U.S. use or usage and so that was one thing that we did, you know, we do look at a lot and consider that a lot when trying to understand what are the probable risks of the device and of course we looked at how we review the devices and how they're intended to be used to assess the probable risks there. And for many of the devices, they are cleared with a tool claim and have specific indications that lead to specific benefits and a lot of that is found in some of the labeling.

So we really also had to rely on the literature to understand what that probable benefit is and how it's being used and when we -- you know, this is kind of a comment for -- the question of effectiveness did come up in kind of all three of the topics today. In general, we try to look at what are the probable benefits and how that relates with the probable risks with the understanding that there are areas of uncertainty and in some cases considerable uncertainty in the evidence for effectiveness and that could be the methods, the findings, what we consider to be a clinical benefit or not. And so we tried to summarize, as best we could, our thoughts on what we found for this, but we'll certainly take all of your comments and your perspectives into account when we debrief internally, too.

DR. JENSEN: That's great. Thank you very much.

So I think we've answered all of the questions. I would like to ask our representatives if they have any additional comments. Let's start with Ms. Edwards. Unmute yourself.

MS. EDWARDS: Oh. Well, I think you all have covered all of my concerns, so I don't have anything to say. I don't know who felt that it would go -- it should be level III, because

I do, too.

DR. JENSEN: Thank you very much.

Mr. Wreh, could you have some comments, please?

MR. WREH: Yeah. Thank you, Dr. Jensen. I'm a non-voting member, but I'll just comment. You know, I'm hearing from the panelists, the voting members. I'll say I agree with the FDA, the device should be classified as Class II 510(k) required with recommended -- so I'm pretty comfortable that it should be Class II and put it in a Class III, it would just have to cause manufacturer to go back and do additional work for a product already on the market, you know, to file PMA. It takes time and it's very costly. So I think the class, which is Class II, to recommend, I think, is fine. Thank you.

DR. JENSEN: Thank you for your comments.

We will now hear final summations from the FDA.

Dr. Vivek, you have the floor.

DR. PINTO: Great. Yeah, actually right before that, I did want to let you know we did look back at the vapocoolants and there were some devices that were cleared OTC, so we do want to correct that. It was a few of them. The majority of them are prescription use, but the ones that were over the counter were all surrounding the indications for use for sports injuries rather than use for injection, surgical use, and we were talking about with the mucous membranes and open wounds, those were still restricted to prescription use. However, we're still going to take your suggestions to consider what we can do to help mitigate the risks of abuse for that type of -- I guess, you know, the ingredients there.

But in summation, this really marks like a milestone for our office, in particular, the division that I run, and there's some additional product codes we're reviewing tomorrow together, but this has been an activity we needed to do and wanted to for several years, actually several decades, but the last few years to really finish up and we really appreciate

all your contributions in the effort to do this, it's going to help with our efficiency in reviewing these devices and determine the attention for resources for these products that we need to give.

And also, any time we get together like this, it just expands our network, like we said before, where we get more perspectives from subject matter experts and different considerations to help in a determination. So thank you, everybody, for all you've done today.

DR. JENSEN: Well, thank you very much. It's been a very interesting experience for me and I hope for the rest of the panelists, too. I understand some of the issues that you're dealing with all of these devices that have been out there since 1976 or before and I think one of the things that came out from this meeting is that we really need to take a look at the efficacy of many of these devices that have been marketed and may need to revisit some of them.

Before I adjourn today's meeting, I'd like to thank all the panelists, our Industry Representative, our Consumer Representative, and of course all the members of the FDA who did all of the presenting today and all of the behind-the-scenes work, you guys do a great job and we really appreciate it.

Tomorrow we'll be looking at three more devices, so we will commence the second half of this public meeting tomorrow promptly at 9:00 a.m. Anybody have anything else they want to say?

DR. PILITSIS: Thanks, Dr. Jensen, for doing an awesome job running the meeting.

DR. JENSEN: Thank you, this has been a real experience. I've enjoyed it. Okay, you all take care, I'll see you all in the morning.

(Whereupon, at 1:14 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:

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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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