SUMMARY MINUTES

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

NEUROLOGICAL DEVICES PANEL

June 3, 2021

Via ZOOM Videoconference

Attendees:

Temporary Chair

Mary Jensen, M.D.
University of Virginia
Charlottesville, VA

Voting Member

Earl Ray Dorsey, M.D., M.B.A.
University of Rochester
Rochester, NY

Temporary Voting Members

Patrick Lyden, M.D.
University of Southern California
Los Angeles, CA

Julie Pilitsis, M.D., Ph.D.
Albany Medical College
Albany, NY

Stavropoula Tjoumakaris, M.D.
Jefferson University Hospitals
Philadelphia, PA

Karen Johnston, M.D., M.Sc.
University of Virginia
Charlottesville, VA

Sujay S. Galen, PT, Ph.D., F.H.E.A.
Byrdine F. Lewis College of Nursing and Health Professions
Atlanta, GA

Stephen McDavitt, PT, DPT, M.S., FAAOMPT, FAPTA
South College
Knoxville, TN

Rory A. Cooper, Ph.D.
University of Pittsburgh
Pittsburgh, PA

David J. Kennedy, M.D.
Vanderbilt University
Nashville, TN

Roberto Ortiz-Aguayo, M.D., M.M.M.
Children's Hospital of Philadelphia
Philadelphia, PA

Industry Representative

Elijah Wreh, M.S.
Regulatory Affairs Manager
Zimmer Biomet

Consumer Representative

Veverly M. Edwards
Patient Safety Advocate/Affiliate Broker
First National Realty

Food and Drug Administration

Vivek Pinto, Ph.D.
Director, Division of Neuromodulation and Rehabilitation Devices

Lin Zheng, Ph.D.
Director, Division of Neurosurgical, Neurointerventional and Neurodiagnostic Devices

Christopher Loftus, M.D.
Office Director (Acting), Neurological and Physical Medicine Devices

Patricio Garcia, M.P.H., CDR, USPHS
Designated Federal Officer

CALL TO ORDER

Panel Chairperson Mary Jensen, M.D., called the meeting to order at 9:01 a.m. She noted the presence of a quorum and affirmed that the Panel members had received training in FDA device law and regulations. She announced that the Panel would be discussing and making recommendations regarding the classification of vapocoolant devices, acupressure devices, and electro-acupuncture stimulators.

PANEL INTRODUCTIONS

Chairperson Jensen asked the Panel members and the FDA staff to introduce themselves.

CONFLICT OF INTEREST STATEMENT

Patricio G. Garcia, M.P.H., CDR, USPHS, Designated Federal Officer, read the Conflict of Interest statement and reported that no conflict of interest waivers had been issued.

He introduced Elijah Wreh, M.S., as the Industry Representative.

OPEN PUBLIC HEARING

Diana Zuckerman, Ph.D., spoke on behalf of the National Center for Health Research. She pointed out that special controls provide some evidence of product safety and reliability, but general controls do not. She asserted that the efficacy of all devices should be verified regardless of price and complexity, and that there is no way of knowing what will happen if similar untested versions of proven devices are put on the market.

CLASSIFICATION AND RECLASSIFICATION OVERVIEW

Megha Reddy explained the three medical device classifications and how they are determined. She then walked the Panel through the classification process for unclassified pre-amendments devices, clarified what input the Agency was seeking, and explained what the next steps will be before the issuance of a final rule.

FDA PRESENTATION

Classification of Vapocoolant Devices Under Product Code "MLY"

Ozell Sanders, M.S., Ph.D., reviewed the indications for use, regulatory history, and clinical background of vapocoolant devices. He gave a device description and presented results from a literature review conducted for the purpose of gathering safety and effectiveness data. He noted that a majority of the publications reported no complications, adverse events, or safety risks from the use of these devices. He also provided background on medical device reports and informed the Panel that a search of agency databases revealed 15 reports of adverse events and two recalls for devices under this product code. He then

reviewed identified risks, mitigations, and proposed special controls. He informed the Panel that the Agency is recommending Class II classification for these devices.

PANEL DISCUSSION/Q&A

Earl Ray Dorsey, M.D., M.B.A., inquired about the use of ethylene chloride as a recreational drug and associated deaths. **Dr. Sanders** confirmed that this is off-label use for these devices, and that one death due to intoxication from chloroethane had been mentioned in the presentation. Dr. Dorsey recommended the inclusion of warnings about inappropriate use in the labeling.

Vivek Pinto, Ph.D., explained that shelf-life stability testing and performance measures are not included in general controls but that they are areas of review for substantial equivalence to predicate devices. He also explained the steps that would be taken to prove non-toxicity of new or different chemicals in experimental devices.

Karen Johnston, M.D., M.Sc., asked if more information could be provided regarding the potential of increased risk to the oral mucosa and to patients with diabetes.

Chairperson Jensen added that there was no data on risks associated with open wounds.

Julie Pilitsis, M.D., Ph.D., asked if the asthma and death complications were connected to use in the mucous membrane. She also asked for information on issues related to use of the device with electrocautery.

Sujay S. Galen, PT, Ph.D., F.H.E.A., requested information on duration of exposure.

Rory A. Cooper, Ph.D., suggested that the risk of flammability be taken into consideration.

David J. Kennedy, M.D., pointed out that there was no reference to myofascial pain in the indications.

FDA QUESTIONS

Dr. Sanders read Question 1: FDA has identified risks to health for vapocoolant devices. These identified risks include pain or discomfort, skin irritation, and thermal injury. Additional risks include electrical shock or burn, interference with other devices, device failure and malfunction leading to ineffective treatment, asthma, and hallucination.

Please comment on whether you agree with 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.

A straw vote requested by the Chair indicated that the Panel agrees with the inclusion of the identified risks.

Chairperson Jensen noted that additional risks mentioned by Panel members include those associated with use in patients with diabetes or other types of peripheral neuropathies, and use on the oral mucosa and on open wounds. Additional concerns raised by Panel members include the need for better guidance when used with electrocautery; warnings of potential death, if inhaled; inclusion of dose and duration recommendations; and warnings

regarding the risk of flammability.

Dr. Sanders read 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
- if, in addition, 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 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 believe can both be mitigated through appropriate labeling.

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:

1. Non-clinical performance testing must characterize the change in skin surface temperature control when the device is used as intended.
2. Non-clinical 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 in breathing.
    f. A warning that the device should not be directly inhaled, as this may be harmful or fatal.

Patrick Lyden, M.D., suggested that other substances could be mixed with ethylene chloride to give it an unpleasant smell as a way of preventing abuse.

Roberto Ortiz-Aguayo, M.D., recommended a pictorial approach in the labeling for certain types of dangers such as flammability and risk of poisoning.

Dr. Cooper advised that some patients may need a hypoallergenic version.

Chairperson Jensen noted that additional topics discussed by the Panel include shelf-life testing, device testing for quality control, and steps that should be taken for similar devices with different chemicals.

Dr. Sanders read Question 3: Please discuss whether you agree with FDA's proposed classification of Class II with special controls for vapocoolant devices. If you do not agree with FDA's proposed classification, please provide your rationale for recommending a different classification.

A straw vote requested by the Chair indicated that the Panel is in favor of Class II classification with special controls.

FDA PRESENTATION

Classification of Acupressure Devices Under Product Code "MVV"

Mary Keszler, M.D., gave a device description and reviewed the indications for use, regulatory history, and clinical background of acupressure devices. She then presented results from a literature review conducted for the purpose of gathering safety and effectiveness data for these devices. She reported that all adverse events were mild in nature and were easily resolved. She also provided background on medical device reports and recalls, noting that one Class II recall had been verified. She informed the Panel that pain, discomfort, and skin irritation have been identified as risks; that FDA believes they can be sufficiently mitigated by general controls; and that Class I classification is recommended.

PANEL DISCUSSION/Q&A

Dr. Lyden asked how many of the studies had placebo controls. **Dr. Keszler** informed him that 26 were RCTs and two were prospective trials. **Chairperson Jensen** noted that there was no statistically significant difference in five of the chemotherapy studies that were compared to a sham wristband.

She also asked if device placement information could be included in the instructions for use and if this would be considered a special control. **Sergio de del Castillo** specified that adequate directions for use is a requirement in all labeling, including Class I.

FDA QUESTIONS

Dr. Keszler read Question 1: 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.

Chairperson Jensen noted that the main issue appears to be appropriate placement.

Veverly M. Edwards, Consumer Representative, asked if there is risk of infection. **Dr. Keszler** confirmed that there were reports of skin irritation, but no evidence of infection.

Allergic reactions, use on open wounds, and persistent nausea were also suggested as additional risks by Panel members.

Dr. Keszler read 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
- if, in addition, 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. 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 these devices. If you do not agree with FDA's proposed classification, please provide your rationale for recommending a different classification.

A straw vote requested by the Chair indicated that the Panel is in favor of Class I classification with general controls.

Dr. Lyden recommended data quality analysis and cautionary advice regarding inadequate information.

Dr. Cooper emphasized the need for further studies and additional data.

Chairperson Jensen summarized the Panel's response:

- Acupressure devices should be classified as Class I; labeling should include a warning that efficacy has not been proven.
- More data is needed to determine which indications do or do not benefit from the use of these devices.

FDA PRESENTATION

Classification of Electro-Acupuncture Stimulators Under Product Code "BWK"

Robert Stefani, Ph.D., gave a device description and reviewed the indications for use, regulatory history, and clinical background of electro-acupuncture stimulators. He then presented results from a literature review conducted for the purpose of gathering safety and effectiveness data. He informed the Panel that 17 of the 28 reviewed studies reported adverse events associated with EA stimulation and that the three most frequently reported events were mild exacerbation of chemotherapy-induced nausea and vomiting, skin pallor, and skin pigmentation. He noted that the evidence strongly indicates that EA stimulation has a significant effect on musculoskeletal pain, postoperative pain, analgesic reduction, and neuropathic pain compared to sham and control groups.

He emphasized that 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. He also provided background on medical device reports and recalls, noting that a review of the Medical Device Recall database found no recalls for devices under this product code. He informed the Panel that adverse tissue reaction, infection, injury or discomfort, and user error have been identified as risks; that FDA believes they can be mitigated by special controls in addition to general controls; and that Class II classification with special controls is recommended.

PANEL DISCUSSION/Q&A

Dr. Stefani specified that the deaths referred to in the presentation were related to the use of needles and not to electrical stimulation. He further clarified that none of the currently cleared devices are indicated for stroke.

Chairperson Jensen pointed out that the use of needles other than those provided in a kit would raise sterility issues.

Dr. Stefani agreed that manufacturers need to identify which electrodes should be used with their devices. He emphasized that this subject could be addressed in labeling and special controls.

Stephen McDavitt, PT, DPT, M.S., advised that the use of textured or un-textured needles should be taken into consideration, and that all needles need to be checked while the device is on.

Dr. Cooper stated that microshock is a hazard that should be recognized and included in the risk assessment.

Dr. Kennedy pointed out that there is insufficient data on the therapeutic effects.

Dr. Dorsey remarked that these devices should not be on the market because of safety issues and lack of effectiveness.

FDA QUESTIONS

Dr. Stefani read Question 1: 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

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 devices.

Chairperson Jensen summarized the Panel's previous discussion:

- The devices should be packaged with all components and marketed for acupuncture only.
- Needles should remain in the subcutaneous region and should not be placed into muscle.
- Operators should be aware of the type of needles that are being used.
- Controls for shock hazards should be put into place.
- Labeling should include warnings about inappropriate use that can lead to death.

Dr. Stefani read 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
- if, in addition, 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.

Identified Risk:
- Adverse tissue reaction

Recommended Mitigation Measure:
- Biocompatibility evaluation
- Labeling

Identified Risk:
- Infection

Recommended Mitigation Measure:
- Sterilization validation
- Cleaning validation
- Shelf life testing
- Labeling

Identified Risk:
- Patient injury or discomfort, including:
  - Electrical shock or burn
  - Bleeding

Recommended Mitigation Measure:
- Electrical, mechanical, and thermal safety testing
- Electromagnetic compatibility (EMC) testing • Non-clinical performance testing
- Software validation, verification, and hazard analysis
- Labeling

Identified Risk:
- User error

Recommended Mitigation Measure:
- Labeling

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:

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. Non-clinical performance testing of the device and electrodes must be conducted to validate the specified electrical output and duration of stimulation of the device.
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. A warning stating that the device is only for use on clean, intact skin;
    c. A detailed summary of the electrical output and the device technical parameters;
    d. A shelf life for the device and accessories;
    e. A statement that sterile components are intended for single use only; and
    f. Instructions on care and cleaning of the device for reusable components.

Dr. Ortiz-Aguayo suggested the inclusion of compatibility information.

Chairperson Jensen noted that the Panel concurs with the proposed special controls. She re-emphasized the Panel's concern regarding appropriate placement of electrodes.

Dr. Stefani read Question 3: Please discuss whether you agree with FDA's proposed classification of Class II with special controls for electro-acupuncture stimulators. If you do not agree with FDA's proposed classification, please provide your rationale for recommending a different classification.

Dr. Lyden remarked that there is a sufficient amount of evidence showing lack of efficacy. He questioned how the Panel could believe that the risks are outweighed by a clinical benefit.

Dr. Galen agreed. He stated that Class II classification would be appropriate with the acknowledgement that there is a lack of effectiveness data.

Drs. Pilitsis and **Ortiz-Aguayo** agreed.

The Panel then discussed whether the lack of effectiveness data plus the identified risks could constitute Class III classification.

Dr. Dorsey pointed out that there is inadequate information for determining whether general controls are sufficient, and that the device presents a potential unreasonable risk of injury or illness.

Dr. Lyden reasoned that even a very small amount of risk would override the equation since there is no benefit.

Dr. Kennedy stated that there is strong evidence showing that the device does not work, that there is a level of risk, and that he would be in favor of Class III.

Dr. Ortiz-Aguayo concluded that there are compelling arguments for Class III and that he would be in favor of it.

Dr. Galen stated that there is a need for more evidence of effectiveness, that there are recommended mitigations, and that he would still be in favor of Class II classification.

FINAL COMMENTS

Ms. Edwards agreed that electro-acupuncture devices should be in Class III.

Elijah Wreh, M.S., Industry Representative, observed that Class III classification is costly and would pose an additional burden on manufacturers for products that are already on the market.

FDA SUMMATION

Dr. Pinto specified that a few of the vapocoolants are cleared OTC devices used primarily for sports injuries, that the majority are for prescription use, and that suggestions regarding the risks of abuse would be taken into consideration. He thanked the Panel members for their contributions.

ADJOURNMENT

Chairperson Jensen thanked the Panel and the FDA staff. She noted that three more devices would be discussed on Day 2. She then adjourned the meeting at 1:14 p.m.

I certify that I attended this meeting on June 3, 2021 and that these minutes accurately reflect what transpired.

James P. Swink -S

Digitally signed by James P. Swink -S
Date: 2021.07.19 10:28:52 -04'00'

Patricio G. Garcia, M.P.H.
Designated Federal Officer

I approve the minutes of this meeting as recorded in this summary.

/S/

Mary Jensen, M.D.
Chairperson

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