Device Classification

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Food and Drug Administration

General and Plastic Surgery Devices Panel Meeting

July 29, 2022

What Is the Purpose of This Panel Meeting?

Discuss the available scientific evidence for Optical Diagnostic Devices for Melanoma Detection and Electrical Impedance Spectrometers, which are currently regulated as Class III devices. You will be asked to recommend whether they should remain in Class III, or be reclassified to Class II as Computer-Aided Devices Which Provide Adjunctive Diagnostic Information About Lesions Suspicious for Melanoma

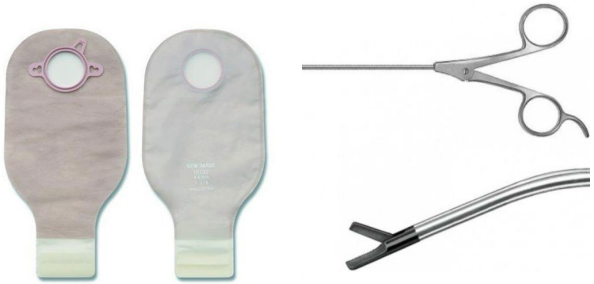
What Are the Device Classes?

- Classified based on controls necessary:
  - Class I (general controls)
  - Class II (special controls)
  - Class III (premarket approval)

A device should be placed in the lowest class whose level of control provides reasonable assurance of safety and effectiveness.

Class I Devices

- Devices for which general controls are sufficient to provide reasonable assurance of the safety and effectiveness
- General controls include:
  - Registration and listing
  - Good manufacturing practices
  - Records and reports
  - Prohibitions against misbranding and adulteration
- Class I devices typically do not require FDA premarket review prior to being marketed

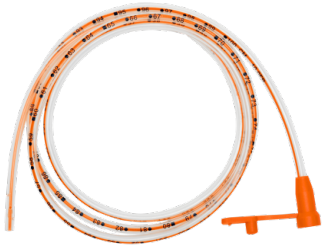


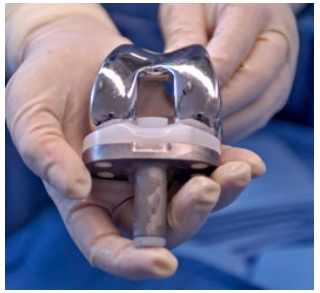
Class I Devices

- Devices which cannot be classified into Class III:
  - Because they are not life-sustaining, life-supporting, of substantial importance in preventing impairment of human health, and
  - Because they do not present a potential unreasonable risk of illness or injury
- Devices which cannot be classified into Class II:
  - Because insufficient information exists to establish special controls to provide a reasonable assurance of safety and effectiveness

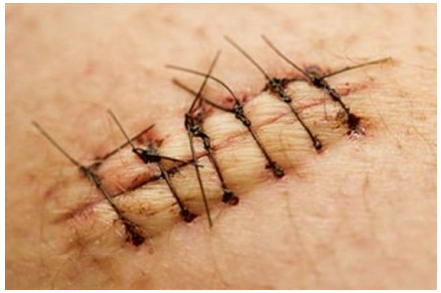
Class II Devices

- Cannot be classified into Class I:
  - because general controls are insufficient to provide reasonable assurance of the safety and effectiveness, and
  - for which there is sufficient information to establish special controls to provide such assurance





- Special controls can include:
  - Performance testing
  - Sterilization validation
  - Device-specific labeling requirements



- These special controls, in combination with the general controls, provide reasonable assurance of safety and effectiveness

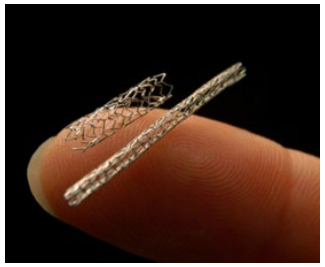
Class II Devices

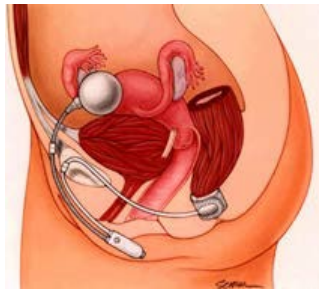
- Class II devices typically require premarket notification to FDA (i.e., a 510(k)) prior to being marketed

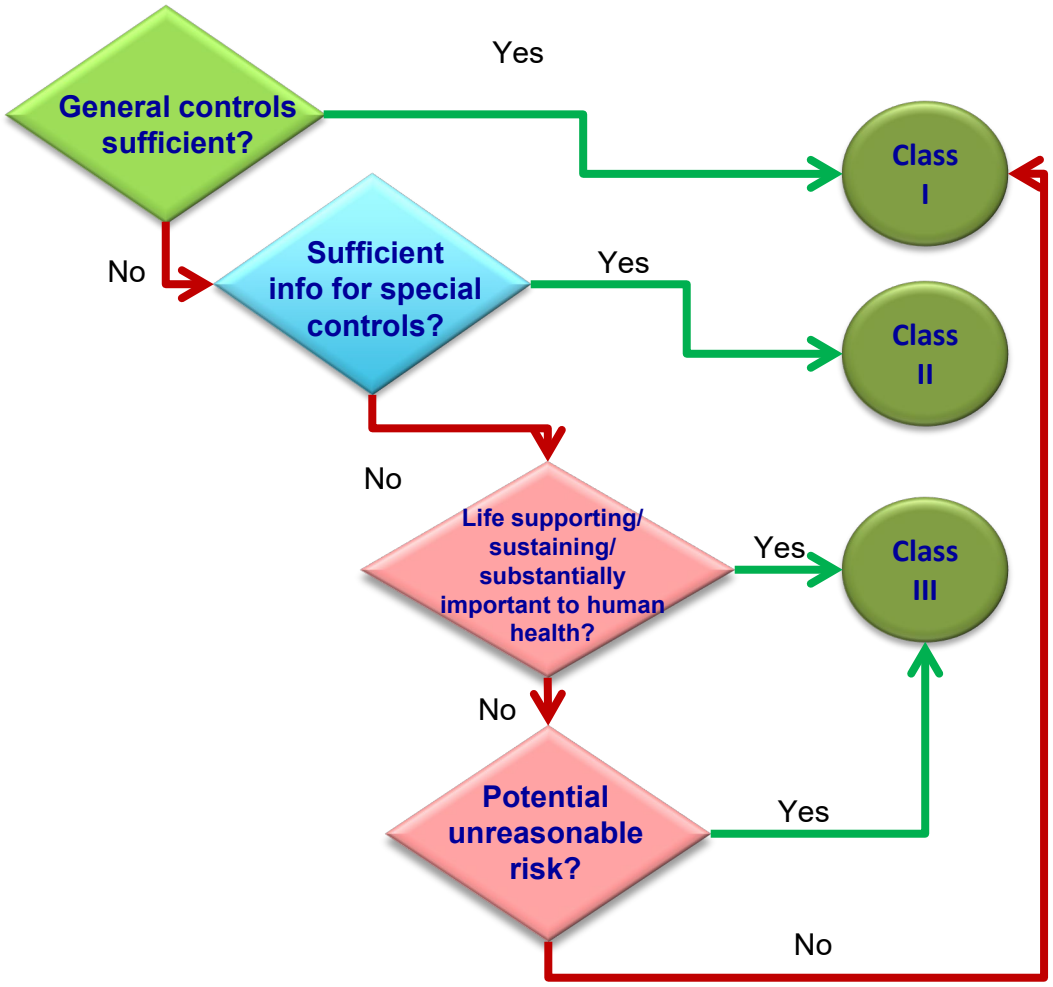
- Companies must provide evidence in their 510(k) submissions of how the special controls were addressed

Class III Devices

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






General controls sufficient?
Yes
Class I
No
Sufficient info for special controls?
Yes
Class II
No
Life supporting/ sustaining/ substantially important to human health?
Yes
Class III
No
Potential unreasonable risk?
Yes
No

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Discuss the available scientific evidence Optical Diagnostic Devices for Melanoma Detection and Electrical Impedance Spectrometers, which are currently regulated as Class III devices. You will be asked to recommend whether they should remain in Class III, or be reclassified to Class II as Computer-Aided Devices Which Provide Adjunctive Diagnostic Information About Lesions Suspicious for Melanoma

What Is the Process?

Decision to start process is based on new information about the device, either on FDA's own initiative or upon the petition of an interested person. The Agency considers intended uses which have been reviewed by the Agency.

- Publish a proposed order announcing our proposed classification and seeking public comment
  - Proposed order published 6/30/22
- Convene a panel meeting to discuss proposed classification
  - Completed today.
- Consider public comments and all available information, including panel recommendations, prior to issuing a final order

What We Need from the Panel

- Review and discuss available scientific evidence regarding safety and effectiveness of Optical Diagnostic Devices for Melanoma Detection and Electrical Impedance Spectrometers
- Input and recommendations should include:
  - Identification of the risks to health presented by the device
  - Whether the device is life-supporting/life-sustaining, of substantial importance in preventing impairment of human health, or presents a potential unreasonable risk of illness or injury
  - Whether sufficient information exists to develop special controls
  - Identification of special controls
  - Whether general controls alone are sufficient

What Will Happen After This Panel Meeting?

- FDA will consider the available evidence, including the input of this panel and the public comments

- FDA will issue a final order identifying the appropriate class
  - If Class I, devices may continue to be marketed
  - If Class II, existing devices may remain on the market provided they meet the designated special controls
  - If Class III, devices may continue to be marketed


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FDA-Approved Computer-Aided Adjunctive Devices for Lesions Suspicious for Melanoma

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Team Leader, Cancer Diagnostics and Treatment Devices
Office of Surgical and Infection Control Devices
Center for Devices and Radiological Health
Food and Drug Administration

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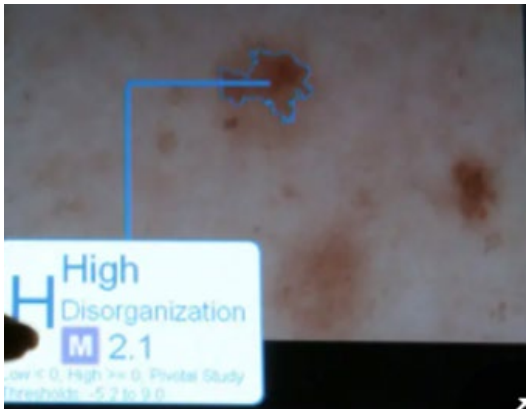
Two Approved PMA Devices

- **MelaFind (P090012)**
  - Reviewed at Panel Meeting 2010
  - Panel recommendations led to revisions in labeling
  - PMA approved 2011
  - First diagnostic device for melanoma – considered high risk
  - Not currently marketed

- **Nevisense (P150046)**
  - PMA approved 2017
  - First electrical impedance spectrometer for melanoma

MelaFind Device Description

- Non-invasive optical diagnostic device
- For use on lesions suspicious for melanoma
- Handheld imager applies light at 10 wavelengths (430-950nm)



Images with permission of Strata Skin Sciences

MelaFind Device Description

- Captures image at each wavelength
- AI/ML analyzes 3D morphological disorganization
- Output:
  - Melafind Positive = high grade dysplasia or melanoma
  - Melafind Negative = not high grade dysplasia or melanoma
  - Risk score (10-point scale)

Fink et al., JDDG 2017

MelaFind Intended Use

- Adjunctive information for dermatologist
- To aid decision to biopsy
- For pigmented lesions deemed suspicious for melanoma, with certain limitations
- Should NOT be used to confirm diagnosis of melanoma
- One element of overall clinical assessment

MelaFind Performance Testing

- Prospective, multi-center, blinded clinical study, 1383 patients
- Suspicious lesions photographed, MelaFind applied (output not visible)
- Dermatologist level of suspicion for MM recorded
- All study lesions were biopsied
- Pathology reviewed by ≥2 blinded central dermatopathologists
- No adverse events

MelaFind Performance Testing

- **Primary Aim 1:** Sensitivity ≥95% at 95% CI – met

	Sensitivity	**95% CI**	
MelaFind	98.3%	94.1%	99.7%

- **Primary Aim 2**: Specificity superior to study dermatologists – met

	Specificity	**95% CI**	
MelaFind	10.6%	9.7%	13.2%
Study Dermatologists	5.5%	4.5%	7.3%
Difference	5.1%	3.3%	7.7%

MelaFind Performance Testing

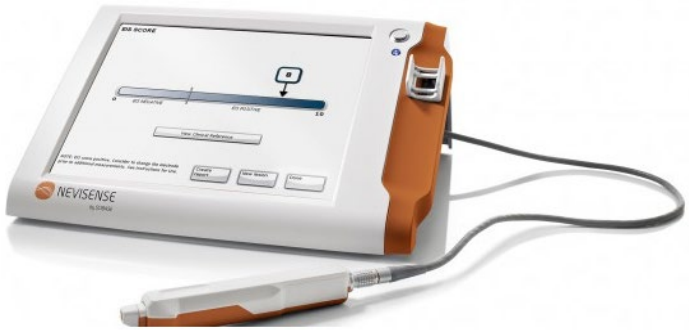
- Reader study
- Compare sensitivity/specificity of MelaFind to providers
- Evaluated photos + dermoscopy + patient history
- Results:
  - Sensitivity, defined as correct decision to biopsy:
    - MelaFind 97%
    - Dermatologists 72% ($p<0.0001$)
  - Specificity
    - MelaFind 9%
    - Dermatologists 51%

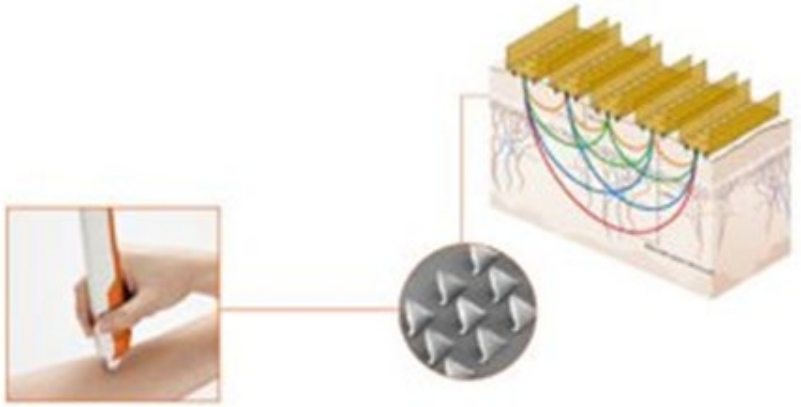
MelaFind 2010 Panel Discussion

- Risk of false negatives a significant safety concern
- Mitigations:
  - Device sensitivity
  - Labeling
  - Intended user: dermatologists trained in use of device
  - Intended use: to provide adjunctive information in decision to biopsy
  - Mandated post-approval study

Nevisense Device Description

- Electrical impedance spectrometer
  - Low electric current
  - Compares tissue impedance in lesion and perilesional skin
- AI/ML analysis of signals
- Output:
  - Score 1-10 (score 3.5+ considered "positive")
  - PPV/NPV of score





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Nevisense Intended Use

Similar to MelaFind:

- Adjunctive information for dermatologist
- To aid decision to biopsy
- For skin lesions deemed suspicious for melanoma, with certain limitations
- Should NOT be used to confirm diagnosis of melanoma
- One element of overall clinical assessment

Nevisense Study

Malvehy, J., et al., Clinical performance of the Nevisense system in cutaneous melanoma detection: an international, multicentre, prospective and blinded clinical trial on efficacy and safety. Br J Dermatol, 2014

- 1951 patients
- Investigators blinded to Nevisense output
- All study lesions biopsied, reviewed by 3 pathologists
- Safety: No serious adverse events

- **Sensitivity 96.6%**
- **Specificity 34.4%**

Summary

- MelaFind and Nevisense are computer-aided adjunctive diagnostic devices
- Intended Use specific to melanoma lesions and decision to biopsy
- FDA has cleared AI/ML-based diagnostic devices as Class II
  - Radiology, gastroenterology
  - Special controls drafted to mitigate risks
- AI/ML-based smartphone Apps (OUS) - low risk medical devices

Summary

- Propose to reclassify devices like MelaFind and Nevisense (adjuncts to melanoma diagnosis) from Class III PMA to Class II with Special Controls

- Panel will be asked whether these two devices should be re-classfied

- Panel will be asked about the proposed Special Controls


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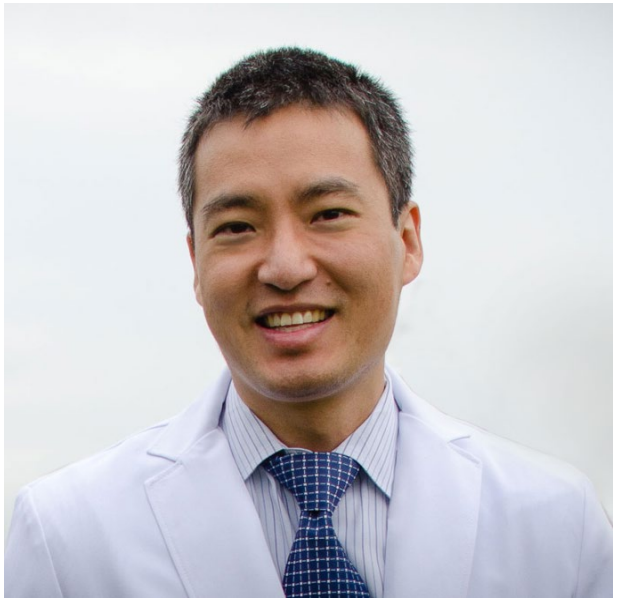
Post-Market Safety and Effectiveness



Henry Lee, M.D.

Medical Officer, Light-Based Devices Team

Office of Surgical and Infection Control Devices
Center for Devices and Radiological Health
Food and Drug Administration

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Methodology

- Post-Market safety and effectiveness:
  - Post-approval studies
  - Peer-reviewed literature
  - MDR, MAUDE, and recall databases

MelaFind Post-Approval Studies

- Assess MelaFind as adjunct to provider
  - Changed provider decision to biopsy 32.5%
  - Increased provider sensitivity by 2%
  - Specificity not assessed
- Standalone performance
  - MF+ output = 79% of lesions
  - Among MF+ lesions, 19% ultimately melanoma or high-grade lesions

Literature Review - MelaFind

- Hauschild et al (2014)
  - Impact of MelaFind on biopsy decisions
  - Increased dermatologists' sensitivity from **69.5% to 78%**
  - Decreased dermatologists' specificity from **55.9% to 45.8%**

A. Hauschild, et al. To excise or not: impact of MelaFind on German dermatologists' decisions to biopsy atypical lesions. *Journal der Deutschen Dermatologischen Gesellschaft*. 12(7):606-614. June 2014.

Literature Review - MelaFind

- Winkelmann et al (2017)
  - Review of 7 studies evaluating MelaFind
  - Aggregate sensitivity improved from **70% to 88%**
  - Aggregate specificity improved from **52% to 58%**
  - Biopsy accuracy increased from **59% to 69%**

R.R. Winkelmann, A.S. Farberg, A.M. Glazer, et al. Noninvasive technologies for the diagnosis of cutaneous melanoma Dermatol Clin, pp. 453-456, 35 (4) (2017),

Post-Market Reports

- MDR/MAUDE:
  - No adverse event reports for MelaFind or Nevisense
- Recall database:
  - Nevisense: none
  - MelaFind: one recall in 2015 – unapproved change in user interface
    - Affected 65 units
    - Addressed in PMA supplement
    - Ended May 4, 2016

Conclusion

- Premarket and postmarket evaluation of the MelaFind and Nevisense did not reveal significant safety concerns

- Class II with special controls will provide a reasonable assurance of safe and effective use of the devices and mitigate the risks to health


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Device Classification and Reclassification Overview

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Assistant Director

Cancer Diagnosis and Treatment Team

Office of Surgical and Infection Control Devices
Center for Devices and Radiological Health
U.S. Food and Drug Administration

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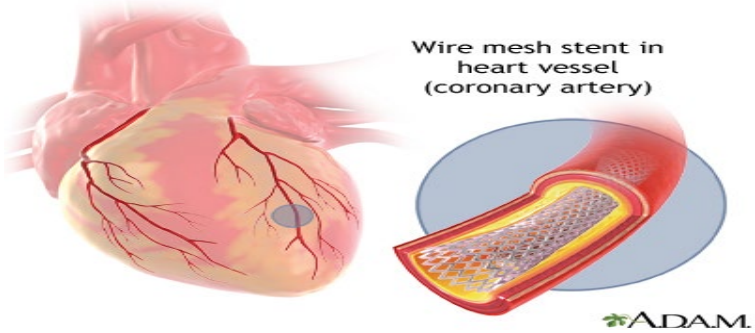
FDA Device Classifications

CLASS I

CLASS II

CLASS III



Strike the Right Balance

CDRH 2015 strategic priority, “Strike the Right Balance Between Premarket and Post market Data Collection”

AI/ML technologies and their output are understood

Training, Validation, False Positive, False Negative

Methodologies to assess performance of these devices are understood

Sensitivity, Specificity, user improvement

Significant advances in AI/ML Technolgies in recent years

10,000s of publications on AI/ML in medical applications

Strike the Right Balance

AI/ML radiology and gastroenterology devices provide adjunctive diagnostic information for cancerous lesions under class II

Risks of Melafind & Nevisense type devices

- Technical review of the safety of the hardware and software
- Greater risk is the false negative output
- Additional risk of false positive output

Assessing Performance

Valid scientific evidence to describe the device performance.

- Clinical data
- Statistics
- Software V&V

Sensitivity and Specificity are high enough

Assuring the device technology is safe to use

- Biocompatibility
- Electrical
- Mechanical

Having appropriate Special Controls

Proposed Reclassification

- FDA is proposing to create a separate classification regulation for computer-aided devices for adjunctive diagnosis of lesions suspicious for melanoma that will be reclassified from class III to II.
- Reclassification of these device types will be prescription use.
- Premarket notification is necessary for these device types

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Thank You

Proposed Reclassification and Regulatory Controls

Scott L. Kominsky, Ph.D.

Biologist/Lead Reviewer, Cancer Diagnostics and Treatment Devices
Office of Surgical and Infection Control Devices
Center for Devices and Radiological Health
Food and Drug Administration

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Proposed Reclassification and Regulatory Controls

Class II device:

- General and Special Controls are sufficient to provide reasonable assurance of safety and effectiveness
  - Probable benefits outweigh probable risks
  - No unreasonable risk of illness or injury
  - Clinically significant results in significant portion of target population

Special Controls

Potential Special Controls

- Performance standards
- Performance testing
- Post-market surveillance
- Patient registries
- Guidelines and recommendations
- Other appropriate actions deemed necessary by the Commissioner

Proposed Special Controls

- Performance testing
- Labeling requirements

Proposed Special Controls

Identified Risks to Health	Mitigation Measures
False negative or false positive results ↓ Delayed diagnosis Increased use of Healthcare resources Unnecessary medical procedures	• Clinical performance testing ○ May include: ○ Standalone testing of sensitivity/specificity ○ Side-by-side comparison ○ Reader study ○ Provides improved assisted-read detection or diagnostic characterization of lesions suspicious for melanoma compared to characterization of lesions without the device

Proposed Special Controls

Identified Risks to Health	Mitigation Measures

False negative or false positive results
 	
↓
 	
Delayed diagnosis
 	
Increased use of Healthcare resources
 	
Unnecessary medical procedures
	• Non-clinical performance testing
	  ○ Performs as intended under the anticipated conditions of use including testing of safety features intended to mitigate device-specific hazards
	• Labeling
	  ○ Detailed instructions for use
	  ○ Information on expected device performance on a dataset representative of the intended population

Proposed Special Controls

Identified Risks to Health	Mitigation Measures

Improper device use / use error
 	
↓
 	
Delayed diagnosis
 	
Increased use of Healthcare resources
 	
Unnecessary medical procedures
	• Labeling
	  ○ Intended patient population, anatomical sites, lesion types, compatible hardware/image acquisition
	  ○ Foreseeable situations of device failure or poor performance

Proposed Special Controls

Identified Risks to Health	Mitigation Measures

Improper device use / use error
 	
↓
 	
Delayed diagnosis
 	
Increased use of Healthcare resources
 	
Unnecessary medical procedures
	• Labeling
	  ○ Description of device and interpretation of outputs
	  ○ Required user qualifications, including training
	• Human Factors Assessment
	  ○ Intended users correctly use device following training

Proposed Special Controls

Identified Risks to Health	Mitigation Measures
Device failure / Malfunction ↓ Patient injury Delayed diagnosis Increased use of Healthcare resources Unnecessary medical procedures	• Non-clinical performance testing ○ Performs as intended under the anticipated conditions of use including testing of safety features intended to mitigate device-specific hazards • Software verification, validation, and hazard analysis

Proposed Special Controls

Identified Risk to Health	Mitigation Measures

Electrical, thermal, mechanical, or light-related injury
 	
↓
 	
Patient and user injury or discomfort
	• Electrical, mechanical, and thermal safety testing
	
	• Software verification, validation, and hazard analysis
	
	• Labeling
	  ○ Instructions on appropriate use and maintenance
	
	  ○ Warnings and cautions to mitigate any device specific hazards, such as use near the eye

Proposed Special Controls

Identified Risk to Health	Mitigation Measures
Interference with other devices ↓ Patient and user injury	• Electromagnetic compatibility testing ○ Ability of device to function safely and effectively in its intended electromagnetic environment, without introducing excessive electromagnetic disturbances that might interfere with other devices

Proposed Special Controls

Identified Risks to Health	Mitigation Measures

Adverse tissue reaction
↓
Patient injury
	• Biocompatibility evaluation
	• Labeling
	  ○ User qualifications needed for safe use
	  ○ Instructions for device maintenance
	  ○ Validated methods and instructions for reprocessing of any reusable components

Infection and cross contamination ↓ Patient injury	• Sterilization validation • Shelf-life testing • Labeling ○ Validated methods and instructions for reprocessing of any reusable components

Summary

Class II: General and Special controls are sufficient to provide reasonable assurance of safety and effectiveness

Identified Risks to Health	Special Controls
• False negative or false positive results • Improper device use / use error • Device failure / malfunction • Electrical, thermal, mechanical, light-related injury • Interference with other devices • Adverse tissue reaction • Infection and cross contamination ↓ Errors in patient management Patient/User injury	• Performance testing • Labeling requirements

FDA proposes that General and Special controls can provide reasonable assurance of safety and effectiveness


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Questions for the Panel

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Question Overview

1) Health Risks of Skin Lesion Analyzers

2) Proposed Class II Device Criteria

3) Proposed Special Controls

Question 1: Health Risks of Skin Lesion Analyzers

- FDA has identified the following risks to health for computer-aided devices which provide adjunctive diagnostic information to dermatologists about lesions suspicious for melanoma:

  - *False negative or false positive results*
  - *Use error / improper device use*
  - *Device failure / malfunction*
  - *Electrical, thermal, mechanical, or light-related injury*
  - *Interference with other devices*
  - *Adverse tissue reaction*
  - *Infection / cross contamination*

- **Please comment on whether this list completely and accurately identifies the risks to health presented by computer-aided devices which provide adjunctive diagnostic information to dermatologists about lesions suspicious for melanoma.**
- **Please comment on whether you disagree with inclusion of any of these risks, or whether you believe that any other risks should be included in the overall risk assessment of this device type.**

Question 2: Proposed Class II Device Criteria

- 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
      - 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
      - does not present a potential unreasonable risk of illness or injury.

Question 2: Proposed Class II Device Criteria

- FDA believes that general controls alone are not sufficient to provide a reasonable assurance of safety and effectiveness for computer-aided devices which provide adjunctive diagnostic information to dermatologists about lesions suspicious for melanoma. **If you disagree, please discuss how general controls alone are sufficient to provide a reasonable assurance of safety and effectiveness for this device type.** General controls may include:
  - Prohibition against adulterated or misbranded devices,
  - Good Manufacturing Practices (GMP),
  - Registration of manufacturing facilities,
  - Listing of device types,
  - Record keeping, etc.

- FDA does not believe that computer-aided devices which provide adjunctive diagnostic information to dermatologists about lesions suspicious for melanoma are "life supporting or life-sustaining, or of substantial importance in preventing impairment of human health." **Do you agree with this assessment? If not, please explain why.**

- FDA does not believe that computer-aided devices which provide adjunctive diagnostic information to dermatologists about lesions suspicious for melanoma present a "potential unreasonable risk of illness or injury" **Do you agree with this assessment? If not, please explain why.**

- FDA believes sufficient information exists to establish special controls for computer-aided devices which provide adjunctive diagnostic information to dermatologists about lesions suspicious for melanoma. Based on the information presented today, **please discuss whether you believe that sufficient information exists to establish special controls that can provide a reasonable assurance of safety and effectiveness for this device type.**

Question 3: Proposed Special Controls

- FDA proposes that the following special controls would adequately mitigate the risks to health and provide reasonable assurance of safety and effectiveness for computer-aided devices which provide adjunctive diagnostic information to dermatologists about lesions suspicious for melanoma:
  - Clinical performance testing will demonstrate acceptable sensitivity and specificity.
  - Non-clinical performance testing will demonstrate acceptable sensitivity and specificity.
  - Non-clinical testing will demonstrate that the device operates as intended under the anticipated conditions.
  - Software validation and verification and cybersecurity testing will be completed in compliance with standards.
  - Thermal, mechanical, electrical, electromagnetic, and light safety testing will be completed in compliance with standards.
  - Biocompatibility, shelf life, and sterilization processes will be demonstrated to comply with standards.
  - Human factors testing and hazard analysis will be performed to acceptable standards.
  - Labeling will provide adequate information on device operation, intended use, intended users (dermatologists), intended patients, intended lesions (pigmented lesions suspicious for melanoma) and body sites, interpretation of output, caution against over-reliance on output, device maintenance and cleaning, and the known sensitivity and specificity of the device.
- **Please discuss whether these special controls appropriately mitigate the identified risks to health of this device type, and whether you recommend additional or different special controls.**


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