FDA Executive Summary
Reclassification Panel Meeting
on Skin Lesion Analyzers

Prepared for the Meeting of the
General and Plastic Surgery Devices
Advisory Panel

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1. Introduction

As required by section 513(e) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the Food and Drug Administration (FDA) is convening the General and Plastic Surgery Devices Advisory Panel (the Panel) to discuss and make recommendations regarding the regulatory reclassification of optical diagnostic devices for melanoma detection (product code: OYD) and electrical impedence spectrometers (product code: ONV) as computer-aided devices which provide adjunctive diagnostic information about lesions suspicious for melanoma.

1.1 Purpose of the Meeting

FDA is holding this Panel meeting to obtain input on the risks and benefits of computer-aided devices which provide adjunctive diagnostic information about lesions suspicious for melanoma. The Panel will discuss and make recommendations to FDA whether these devices should remain in Class III or be reclassified to Class II, considering sufficient information to establish special controls to provide such assurance. FDA is proposing to reclassify optical diagnostic devices for melanoma detection and electrical impedence spectrometers as Class II devices called "computer-aided devices which provide adjunctive diagnostic information about lesions suspicious for melanoma" where FDA will propose special controls that will provide a reasonable assurance of safe and effective use of the device and mitigate the risks to health. If the Panel believes that Class II is appropriate for computer-aided devices which provide adjunctive diagnostic information about lesions suspicious for melanoma, the Panel will also be asked to discuss whether they believe the proposed special controls are adequate to provide a reasonable assurance of safety and effectiveness and mitigation of risks to health.

1.2 Structure of Meeting

The panel meeting will be held in a virtual format over the course of one day and includes time for FDA presentations, open public comment, questions by the panel, and panel deliberation.

The morning session will focus on describing how devices are currently regulated, a description of these devices, the risks to health, and proposed special controls to mitigate the risks. The afternoon will include industry presentations and public comment, the questions for the panel, and panel deliberations.

1.3 Background on the Classification Process

FDA regulates medical devices and categorizes them into one of three classes (I, II, or III).

Class I

Class I devices are subject to the least regulatory controls. They usually present minimal potential for harm to the user and patient and are often simpler in design compared to Class II or Class III devices. Class I devices are subject only to general controls, which include but are not limited to establishment registration and listing; prohibitions against adulteration and misbranding; records and reports; and good manufacturing practices (GMPs). Examples of Class

I devices include elastic bandages, AC powered medical examination light devices, surgical cameras, examination gloves, and manual surgical instruments for general use. Most Class I devices are exempt from premarket review requirements and can therefore be marketed without a premarket submission.

Class II

Class II devices are those devices for which general controls alone are insufficient to provide reasonable assurance of safety and effectiveness, and for which there is sufficient information to establish special controls to provide such assurance. Examples of special controls are performance standards, post market surveillance, patient registries, and special labeling requirements. Special controls may also include specific types of performance testing (e.g., biocompatibility, sterility, electromagnetic compatibility, pre-clinical testing, etc.) which FDA may outline in the regulation. Hence, in addition to complying with general controls, Class II devices are also subject to special controls. Most Class II devices must obtain marketing clearance through premarket notification [510(k)] submissions. Examples of Class II devices include intravascular administration sets (e.g., syringes), laser surgical instruments for use in general and plastic surgery and in dermatology, endoscopes, stereotaxic instruments, and electrosurgical cutting and coagulation devices and accessories.
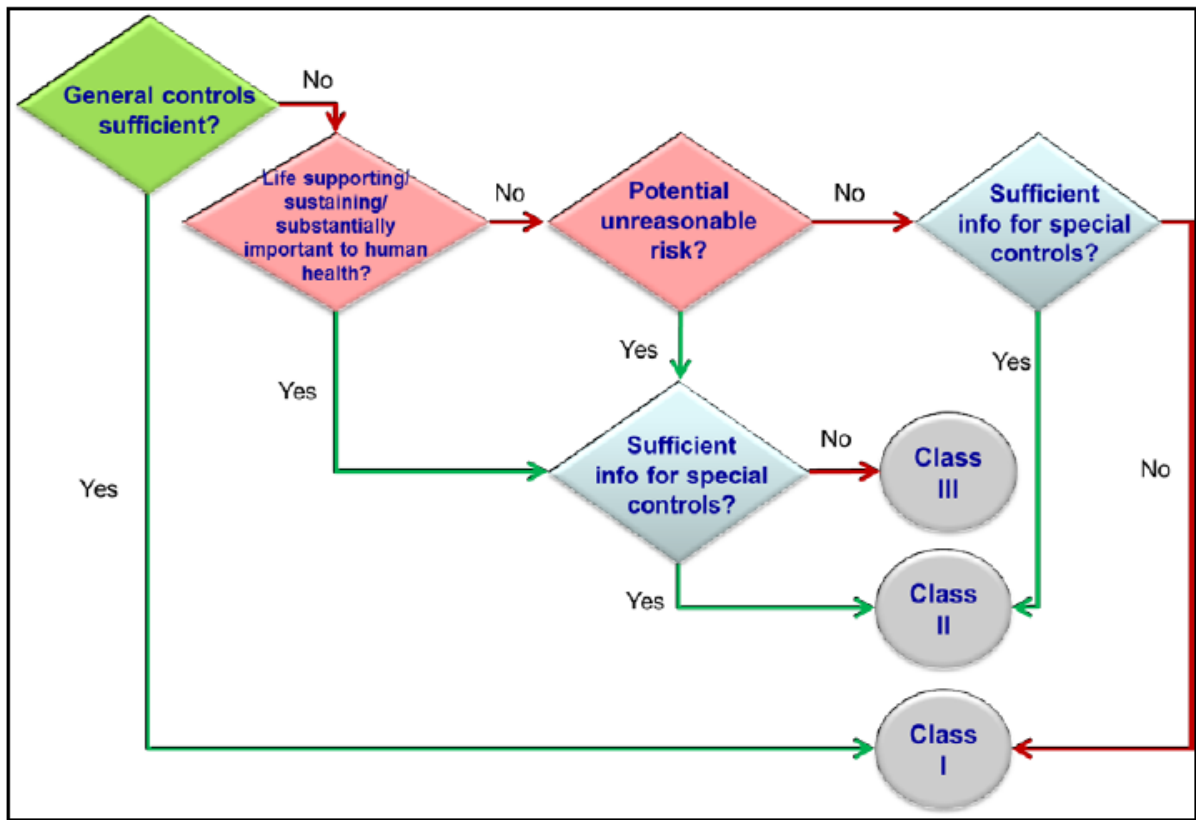
Class III

Class III is the most stringent regulatory category for devices. Class III devices are typically high-risk devices and include devices for which insufficient information exists to provide reasonable assurance of safety and effectiveness solely through general or special controls. All devices that are not substantially equivalent to any existing devices in Class I or II are automatically classified in Class III. Examples of Class III devices include breast implants, dermal fillers, and endodontic dry heat sterilizers. Class III devices typically require marketing approval through a premarket approval (PMA) application.

In accordance with section 513 of the Food, Drug, and Cosmetic Act (FD&C Act), a device should be classified in Class III if:

- the device is purported or represented to be for a use in supporting or sustaining human life, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury, and

- insufficient information exists to determine that general controls and special controls are sufficient to provide reasonable assurance of its safety and effectiveness.

Figure 1: Classification Process

Figure flowchart:

- **General controls sufficient?** — Yes → Class I; No → Life supporting/sustaining/substantially important to human health?
- **Life supporting/sustaining/substantially important to human health?** — Yes → Sufficient info for special controls?; No → Potential unreasonable risk?
- **Potential unreasonable risk?** — No → Sufficient info for special controls?; Yes → Sufficient info for special controls?
- **Sufficient info for special controls?** (center) — Yes → Class II; No → Class III
- **Sufficient info for special controls?** (right) — Yes → Class II; No → Class I

1.4 History of Regulatory Pathway

FDA has approved two computer-aided skin lesion classification devices that provide adjunctive diagnostic information about lesions suspicious for melanoma. They are currently designated class III devices with product codes OYD and ONV and were approved with rigorous pre-market review as well as post-market regulations that are mandated for Class II devices. For these two devices, safety and effectiveness were demonstrated with performance data generated with their own device. There is no predicate device, and therefore data from predicate devices typically cannot be leveraged to justify class III device approval.

Since the approval of MelaFind and Nevisense, there has been a significant increase in the number of publications related to the use of artificial intelligence and machine learning (AI/ML). [1-9] This has resulted in a significant body of knowledge to understand the safety and effectiveness for these technologies, and this knowledge may provide sufficient information to determine that general controls and special controls are sufficient to provide reasonable assurance of their safety and effectiveness.

2. Class III Skin Lesion Analyzers (SLA)

To date FDA has approved two devices, both Class III, that are skin lesion classifiers: MelaFind and Nevisense. They are both intended for use on clinically atypical cutaneous pigmented lesions with one or more clinical or historical characteristics of melanoma, excluding those with a clinical diagnosis of melanoma or likely melanoma. Although these two devices have different technologies for signal detection, e.g., optical versus electrical impedance, they both utilize AI/ML algorithms to analyze images or signals from the skin lesions and to provide a management recommendation (i.e., risk score to support decision to biopsy). This differs from other devices used to assess skin or other tissues, such as dermatoscopes, optical coherence tomography (OCT) devices or reflectance confocal microscopy (RCM) devices in that these imaging devices require the user to assess an image, whereas MelaFind and Nevisense analyze the image or signal and provide a discrete output (whether biopsy or not).

MelaFind (P090012 and supplements) [10]

On June 3, 2009, FDA received a PMA (P090012) from MELA Sciences, Inc. (later STRATA Skin Sciences) for the MelaFind device. MelaFind is a non-invasive optical diagnostic device for melanoma detection. It has a hand-held imager that, when placed on a skin lesion, acquires 10 digital images using light from 430 nm (blue) to 950 nm (near infrared) wavelengths. An AI/ML-based algorithm classifies the image based upon the degree of 3-dimensional morphological disorganization and provide a risk score, on a10-point scale, of the lesion being melanoma or a high-grade melanocytic lesion.

This device is intended to be used by dermatologists trained in the use of the device and is intended for use on clinically atypical cutaneous pigmented lesions with one or more clinical or historical characteristics of melanoma, excluding those with a clinical diagnosis of melanoma or likely melanoma. It is intended to provide adjunctive information to a dermatologist considering biopsy of a suspicious lesion and is not intended to be used to confirm a clinical diagnosis of melanoma. Data provided in the PMA submission supported that there is a reasonable assurance of safety and effectiveness of this device when used as indicated above. The pivotal clinical trial met its primary safety and effectiveness endpoints by achieving a 98.3% sensitivity to malignant melanoma, among lesions with dermatological diagnoses of "Melanoma cannot be ruled out" or "Not melanoma", was at least 95% at a 95% confidence level, and achieved a superior pooled specificity (10.6%) compared to the study dermatologists (5.5%). Additionally, no direct adverse events were reported for the patients enrolled in the MelaFind pivotal study.

An advisory committee meeting was held on November 18, 2010, with the General and Plastic Surgery Devices Panel; the MelaFind PMA was discussed by the panel members. The panel raised a concern regarding the use of the MelaFind device by non-dermatologists and the use of the device by an untrained operator. The panel, as well as the outcome data in the PMA submission, identified false negatives as a potential risk that could result in delayed care, which would be a significant safety concern if unmitigated. The device labeling and intended use

clarification as an adjunct to physician decision making were determined to be appropriate to mitigate this risk This risk was also mitigated by limiting the use of the device to physicians trained in the clinical diagnosis and management of skin cancer (i.e., dermatologists) who have also successfully completed a training program for the device. The indications and labeling were found acceptable and address these outstanding concerns, since lesions that are clinically suspicious for melanoma would not be evaluated by MelaFind, and a MelaFind negative reading would only be part of the assessment for a clinical decision to biopsy and will not replace clinical judgement. CDRH issued an approval order for P090012 on November 1, 2011, with the condition that the Sponsor conduct a post-approval study (PAS). The PAS was terminated in 2016 because the original device was modified in both software and firmware. The safety and effectiveness of the modified device were supported by a reader study (changes approved in PMA supplements P090012/S010, and P090012/S011 in 2016).

MelaFind is the only device under product code OYD was approved with the following Intended Use:

> MelaFind is intended for use on clinically atypical cutaneous pigmented lesions with one or more clinical or historical characteristics of melanoma, excluding those with a clinical diagnosis of melanoma or likely melanoma. MelaFind is designed to be used when a dermatologist chooses to obtain additional information for a decision to biopsy. MelaFind should NOT be used to confirm a clinical diagnosis of melanoma.

> MelaFind is only for use by physicians trained in the clinical diagnosis and management of skin cancer (i.e., dermatologists) who have also successfully completed a training program in the appropriate use of MelaFind.

> The MelaFind result is one element of the overall clinical assessment. MelaFind positive lesions (which may include malignant melanoma, melanoma in situ, high grade dysplastic nevi and atypical melanocytic proliferation/hyperplasia) should be considered for biopsy; the biopsy decision of a MelaFind negative lesion should be based on the remainder of the entire clinical context. Lesions that are "non-evaluable" by MelaFind should be carefully re-evaluated for biopsy.

> MelaFind is indicated only for use on lesions with a diameter between 2 mm and 22 mm, lesions that are accessible by the MelaFind imager, lesions that are sufficiently pigmented (i.e. not for use on non-pigmented or skin-colored lesions), lesions that do not contain a scar or fibrosis consistent with previous trauma, lesions where the skin is intact (i.e., nonulcerated or non-bleeding lesions), lesions greater than 1 cm away from the eye, lesions which do not contain foreign matter, and lesions not on special anatomic sites (i.e., not for use on acral, palmar, plantar, mucosal, or subungual areas). MelaFind is not designed to detect pigmented non-melanoma skin cancers, so the dermatologist should rely on clinical experience to diagnose such lesions

Nevisense (P150046 and supplements)

On December 7, 2015, FDA received a PMA (P150046) from SCIBASE AB for the Nevisense device, an electrical impedance spectrometer for melanoma detection. A handpiece connected to the tabletop device applies low current electrical signals to the skin and measures the impedance (resistance) to the flow of current in the tissue. The tip is placed on normal skin to measure baseline impedance and then on the suspicious lesion. The device screen then provides a score from 0 to 10 that reflects the degree of atypia in the lesion along with the positive and negative predictive value of the score. The device refers to lesions with scores up to 3.5 as "EIS negative" and scores from 3.5 to 10 as "EIS positives."

The pivotal study published in scientific literature focused on the safety and effectiveness of the device for distinguishing benign skin lesions from melanoma. [6] Eligible skin lesions in the study were examined with the device, photographed, excised, and subjected to histopathological evaluation. 1951 patients with 2416 lesions were enrolled; 1943 lesions were eligible and evaluable for the primary efficacy end point, including 265 melanomas. A total of 36 adverse events (AEs) were observed in 28 patients (1.5%), out of which only three AEs that occurred on three patients (0.2%) were defined as definitely related to the device. No serious AEs, serious adverse device effects, or unanticipated adverse device effects were observed. The study concluded that the electrical impedance spectrometer investigated is accurate and safe as a support tool for dermatologists in the detection of cutaneous melanoma because the sensitivity of the device was measured to be 96.6% with a specificity of 34.4%. Nevisense PMA was not on panel track, but after reviewing the totality of the data, on June 28, 2017, FDA issued an approval order for Nevisense.

Nevisense, the only device approved with product code ONV, was approved with the following Intended Use:

> Nevisense is indicated for use on cutaneous lesions with one or more clinical or historical characteristics of melanoma, when a dermatologist chooses to obtain additional information when considering biopsy. Nevisense should not be used on clinically obvious melanoma. The Nevisense result is one element of the overall clinical assessment. The output of Nevisense should be used in combination with clinical and historical signs of melanoma to obtain additional information prior to a decision to biopsy.
>
> Nevisense is indicated only for use on:
>
> - primary skin lesions with a diameter between 2 mm and 20 mm
> - lesions that are accessible by the unique probe
> - lesions where the skin is intact (i.e., non-ulcerated or non-bleeding lesions)
> - lesions that do not contain a scar or fibrosis consistent with previous trauma
> - lesions not located in areas of psoriasis, eczema, acute sunburn or similar skin conditions

- lesions not in hair-covered areas
- lesions which do not contain foreign matter
- lesions not on special anatomic sites (i.e., not for use on acral skin, genitalia, eyes, mucosal areas).

Although these two class III devices have different technologies for signal detection, e.g., optical versus electrical impedance, they both utilize computer algorithms to analyze the signals from the skin lesions. Other devices designed to assess skin lesions which are intended to provide different levels of assistance to healthcare providers in clinical decision making, followed a different regulatory framework.

3. Device Description

Optical diagnostic devices for melanoma detection and electrical impedance spectrometers are post amendment devices classified into class III under section 513(f)(1) of the FD&C Act. An optical diagnostic device for melanoma detection is a prescription device used in the detection of melanoma and high-grade lesions among atypical lesions in order to rule-out melanoma. An electrical impedance spectrometer is a prescription device used on cutaneous lesions with one or more clinical or historical characteristics of melanoma, when a dermatologist chooses to obtain additional information when considering biopsy. It should not be used on clinically obvious melanoma. It is to be used as one element of the overall clinical assessment. The output given by the device should be used in combination with clinical and historical signs of melanoma to obtain additional information prior to a decision to biopsy. Prescription devices are exempt from the requirement for adequate directions for use for the layperson under section 502(f)(1) of the FD&C Act (21 U.S.C. 352(f)(1)) and 21 CFR 801.5, as long as the conditions of 21 CFR 801.109 are met.

MelaFind is a non-invasive optical diagnostic device for melanoma detection. It has a hand-held imager that acquires 10 multi-spectral [from 430 nm (blue) to 950 nm (near infrared)] digital images (1280 × 1024 pixels). An automated (objective) computer-vision system classifies the image of a pigmented skin lesion using fixed algorithms based upon the degree of 3-dimensional morphological disorganization. It is intended for use on clinically atypical cutaneous pigmented lesions with one or more clinical or historical characteristics of melanoma, excluding those with a clinical diagnosis of melanoma or likely melanoma.

NeviSense is an electrical impedance spectrometer. It measures electrical impedance of skin lesions with electrodes containing micro invasive pins that penetrate the stratum corneum. A control unit processes the examination data and provides an output called the electrical impedance spectroscopy (EIS) score. It is indicated for use on cutaneous lesions with one or more clinical or historical characteristics of melanoma, when a dermatologist chooses to obtain additional information when considering biopsy.

These devices are for prescription use. Both devices collect lesion information, optical or electrical impedance, and analyze the data to provide diagnostic information to the user. Computer-aided devices which provide adjunctive diagnostic information about lesions suspicious for melanoma Computer-aided devices for adjunctive diagnosis of lesions suspicious for melanoma can provide earlier diagnosis before final biopsy decision. The information from these SLA provides additional valid scientific output that can improve the user's decisions on next steps of care for a given lesion. Data provides additional valid scientific evidence to support the clinical assessment of the patient lesion and the decision to biopsy.

4. Proposed Reclassification

An optical diagnostic device for melanoma detection is a prescription device used in the detection of melanoma and high-grade lesions among atypical lesions in order to rule-out melanoma. An electrical impedance spectrometer is a prescription device used on cutaneous lesions with one or more clinical or historical characteristics of melanoma, when a dermatologist chooses to obtain additional information when considering biopsy. It should not be used on clinically obvious melanoma. It is to be used as one element of the overall clinical assessment. The output given by the device should be used in combination with clinical and historical signs of melanoma to obtain additional information prior to a decision to biopsy. Prescription devices are exempt from the requirement for adequate directions for use for the layperson under section 502(f)(1) of the FD&C Act (21 U.S.C. 352(f)(1)) and 21 CFR 801.5, as long as the conditions of 21 CFR 801.109 are met.   As part CDRH's 2014-2015 strategic priority "Strike the Right Balance Between Premarket and Post market Data Collection," a retrospective review of class III devices subject to a PMA was completed to determine whether reclassification may be appropriate based on our current understanding of the technology. During this retrospective review, FDA reviewed how skin lesion analyzers are used in clinical decision making, benefits and risks of skin lesion analyzers reported in literature, how the performance of the devices is evaluated, and the information needed to determine whether the device provides a reasonable assurance of its safety and effectiveness. Based on the review, FDA determined that sufficient information exists such that the risks of false positive and false negative results, misuse, and device failure can be mitigated, to establish special controls that, together with general controls, can provide a reasonable assurance of the safety and effectiveness of skin lesion analyzers and therefore proposes these devices be reclassified from class III to class II.

In accordance with section 513(f)(3) of the FD&C Act and 21 CFR part 860, subpart C, FDA is proposing to reclassify the devices under product codes OYD and ONV from class III to class II. FDA believes that there is sufficient information available through FDA's accumulated experience with these devices from review of the original MelaFind PMA submission, peer-reviewed literature, FDA's MDR, MAUDE, and recall databases, and knowledge of similar devices to establish special controls that effectively mitigate the risks to health identified in section V. Absent the special controls identified in this proposed order, general controls applicable to the device are insufficient to provide reasonable assurance of the safety and effectiveness of the device.

FDA is proposing to create a separate classification regulation for computer-aided devices which provide adjunctive diagnostic information about lesions suspicious for melanoma that will be reclassified from class III to II. Under this proposed order, if finalized, these devices currently regulated under product codes OYD and ONV will be identified as a prescription device. As such, the prescription device must satisfy prescription labeling requirements (see § 801.109 (21 CFR 801.109), Prescription devices). Prescription devices are exempt from the requirement for adequate directions for use for the layperson under section 502(f)(1) of the FD&C Act (21 U.S.C. 352(f)(1)) and § 801.5 (21 CFR 801.5), as long as the conditions of § 801.109 are met. In this proposed order, if finalized, the Agency has identified the special controls under section

513(a)(1)(B) of the FD&C Act that, together with general controls, will provide a reasonable assurance of the safety and effectiveness for skin lesion analyzers.

Section 510(m) of the FD&C Act provides that FDA may exempt a class II device from the premarket notification requirements under section 510(k) of the FD&C Act if FDA determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device. For this type of device, FDA has determined that premarket notification is necessary for skin lesion analyzer devices to provide reasonable assurance of the safety and effectiveness. Therefore, the Agency does not intend to exempt these proposed class II devices from 510(k) requirements. Persons who intend to market this type of device must submit a 510(k) and receive clearance prior to marketing the device.

5. Risks to Health

From FDA's experiences over the years in reviewing submissions for skin lesion analyzing devices and similar radiological devices, FDA determined the risks to health associated with skin lesion analyzers including optical devices and electrical impedance analysis devices include the following: (1) False negative results could result in adverse outcomes, including incorrect diagnosis and delay in disease management; (2) False positive results may result in adverse outcomes, such as incorrect management of the patient with possible adverse effects, and unnecessary additional procedures, such as biopsy; (3) The device could be misused to analyze images from an unintended patient population, an unintended anatomical site, or lesion having an unintended attribute, or on images acquired with incompatible imaging hardware or incompatible image acquisition parameters, resulting in possibly poor device performance; (4) The device could be misused by not following the appropriate reading protocol, which may lead to lower accuracy; and (5) Device failure could result in the absence or delay of device output, or incorrect device output, which could likewise lead to inaccurate patient assessment.

6. Summary of Reasons for Reclassification

After considering the risk-related information above, FDA has determined that all class III skin lesion analyzers currently approved by FDA should be reclassified into class II on the basis that special controls, in addition to general controls, can be established to provide a reasonable assurance of the safety and effectiveness of the device. FDA believes that the risks to health associated with skin lesion analyzers which provide adjunctive diagnostic information about lesions suspicious for melanoma can be mitigated with the following special controls to provide a reasonable assurance of its safety and effectiveness:

FDA's reasons for reclassification of these devices are as follows:

- The risk of false positive results and false negative results can be mitigated through clinical performance testing, which may include, for example, standalone test(s) with acceptable performance thresholds (e.g., sensitivity and specificity), side-by-side comparison(s), and/or a reader study, as applicable, as well as non-clinical performance testing. The clinical performance testing must demonstrate that the device improves assisted-read detection and/or diagnostic characterization of lesions suspicious for melanoma compared to characterization of lesions without the device in the indicated user population(s) when used in accordance with the instructions for use. The non-clinical performance testing, among other things, must demonstrate that the device performs as intended under anticipated conditions of use.
- The risk of false positive results and false negative results can be further mitigated by special controls that require information in labeling to provide detailed instructions for use and inform the user of the expected device performance on a dataset representative of the intended population.
- The risk associated with use error and inappropriate use of a computer-aided device which provide adjunctive diagnostic information about lesions suspicious for melanoma can be mitigated by requiring that the following information be included in the device labeling: the intended patient population (e.g., gender, Fitzpatrick Skin Type), anatomical site(s), type(s) of lesions, compatible imaging hardware, and compatible image acquisition parameters needed for the device to achieve its intended use. This risk can be further mitigated by special controls that require the device labeling to inform intended users of foreseeable situations in which the device is likely to fail or not to operate at its expected performance level. The risk resulting from not following the intended reading protocol can be mitigated by requiring that the device labeling include a device description and information needed to facilitate the clinical interpretation of all device outputs, and by special controls requiring that the device labeling provide a description of user training required prior to use. This risk can be further mitigated by special controls that require a human factors assessment to demonstrate that intended users can correctly use the device according to the intended use following user training.
- The risk of device failure or malfunction can be mitigated by requiring non-clinical performance testing and software verification, validation, and hazard analysis, and by requiring that information needed to facilitate the clinical interpretation of all device outputs be included in the labeling (e.g., negative/positive result, risk score). This risk can be further mitigated by special controls that require the device labeling to inform intended users of foreseeable situations in which the device is likely to fail or not to operate at its expected performance level.

- The risk of electrical, thermal, mechanical and light-related hazards leading to user injury or discomfort can be mitigated by special controls that require testing that demonstrates electrical, mechanical, and thermal safety; software verification, validation and hazard analysis; and device labeling that includes instructions on appropriate usage and maintenance of the device. The risk of eye injury due to energy (e.g., light) exposure can be mitigated by special controls that require labeling that warns users about exclusion of lesions close to the eye and unsafe energy exposure to the eyes.
- The risk that the device may interfere with other devices due to radiofrequency or electromagnetic interference can be mitigated by requiring testing that demonstrates electromagnetic compatibility.
- The risk of adverse tissue reaction for patient-contacting devices can be mitigated by special controls that require elements of the device that may contact the patient to be demonstrated to be biocompatible and labeling that includes, in addition to user qualifications needed for safe use of the device, instructions for device maintenance and validated methods and instructions for reprocessing of any reusable components.
- The risks of infection and cross contamination for patient-contacting components can be mitigated by special controls that require sterilization validation, shelf-life testing, and labeling that includes validated methods and instructions for reprocessing of any reusable components.

7. Summary of Data Upon Which the Reclassification Is Based

FDA has considered and analyzed the peer-reviewed literature, FDA's publicly available MDR, MAUDE, and Medical Device Recall databases, and knowledge of similar devices.

Peer-reviewed Literature

FDA performed a literature search to evaluate data related to optical diagnostic devices for melanoma detection. Published data was found in literature relevant to optical diagnostic devices for melanoma detection and for electrical impedance spectrometers.

The clinical performance for an electrical impedance spectrometer was assessed in a multicenter, prospective, blinded clinical trial, published in 2014 (Ref. 2). This study focused on the safety and effectiveness of the device for distinguishing benign skin lesions from melanoma. Eligible skin lesions in the study were examined with the device, photographed, excised, and subjected to histopathological evaluation. 1951 patients with 2416 lesions were enrolled; 1943 lesions were eligible and evaluable for the primary efficacy end point, including 265 melanomas. A total of 36 adverse events (AEs) were observed in 28 patients (1.5%), out of which only three AEs that occurred on three patients (0.2%) were defined as definitely related to the device. No serious AEs, serious adverse device effects, or unanticipated adverse device effects were observed. The study concluded that the electrical impedance spectrometer investigated is accurate and safe as a support tool for dermatologists in the detection of cutaneous melanoma because the sensitivity of the device was measured to be 96.6% with a specificity of 34.4%.

Reviews of skin cancer detection technologies conclude that optical diagnostic information devices for melanoma detection and electrical impedance spectrometers are effective as adjunctive sources of information for dermatologists considering biopsy of a lesion to support a diagnosis of a malignant lesion (Refs. 3-5). These reviews acknowledge that the specificity of these devices can be relatively low, but that the low specificity and low positive predictive value is acceptable due to the very high sensitivity and negative predictive value associated with these devices. These reviews reference data supporting that these devices generally are more sensitive than visual inspection of suspicious lesions without magnification and that the benefits of using these devices to provide adjunctive information outweigh the risks related to false positives resulting in unnecessary biopsies because the adjunctive information provided by the device can facilitate detection of malignant lesions that may otherwise go undetected. One review concludes that the use of these devices as part of the biopsy decision making process increases the overall sensitivity for malignant melanoma detection, which justifies the low specificity and high biopsy number due to improved detection of malignant melanoma (Ref. 4). Another review categorizes multispectral optical devices, such as the device approved in PMA P090012, together with electrical impedance spectrometers as appropriate for providing adjunctive information for the assessment of atypical, preselected lesions in order to support clinician decision making. The review notes that the process of selecting lesions for analysis needs an experienced dermatologist trained in operating the device and that these devices do not provide a definitive or final diagnosis (Ref. 5).

The totality of the literature reviewed indicates that false results and unnecessary biopsies are some of the potential risks related to the use of skin lesion analyzers. The literature reviewed support that these risks can be successfully mitigated for these types of devices by ensuring that

the devices are highly sensitive, specifying that the devices are intended to be used to provide adjunctive information for clinical decision making rather than for giving a conclusive diagnosis, and ensuring that the user population consists of dermatologists trained to use the device.

FDA's publicly available MDR, MAUDE, and Medical Device Recall databases

A search of FDA's publicly available MDR database revealed no medical device reports for product codes OYD and ONV, the product codes proposed to be reclassified as computer-aided devices which provide adjunctive diagnostic information about lesions suspicious for melanoma.

A search of FDA's publicly available recall database revealed no entries for devices under the ONV product code and a single entry for a device approved under the OYD product code posted on May 20, 2015. The recall was conducted due to a software change for the device's user interface that was made without submission of a PMA supplement. This recall affected approximately 65 units of the device and was terminated on May 4, 2016.

A search of FDA's publicly available MAUDE database revealed no entries for devices under the OYD product code and a single entry for a device approved under the ONV product code. A review of the single entry in the MAUDE database for the ONV product code revealed that the device subject to the report was misidentified as an electrical impedance spectrometer as described by product code ONV as evidenced by the fact that the event date for the entry is May 14, 2014, which was before any devices were approved under this product code.

Mitigation of Risks to Health/Proposed Special Controls

These devices provided adjunctive information to the dermatologist when they are gathering information to decide to whether to biopsy a lesion suspicious for melanoma. With this additional information the dermatologist makes the decision how to best manage their patient and that lesion. No treatment decisions for care to the patient are made based upon the device output alone. Because the safety and effectiveness of device output are supported by valid scientific evidence that has been reviewed by the FDA, there is reasonable assurance that these devices can be sufficiently regulated in class II with special controls.

When evaluating the adequacy of the special controls, it is important to understand that the FDA relies on the ability of each special control identified to mitigate an identified risk to health. Hence, FDA believes that, in addition to general controls, the special controls identified below are necessary to provide a reasonable assurance of safety and effectiveness for computer-aided devices which provide adjunctive diagnostic information about lesions suspicious for melanoma.

Table 1: Risks to Health and Mitigation Measures for Computer-Aided Devices which Provide Adjunctive Diagnostic Information about Lesions Suspicious for Melanoma

Identified Risk to Health	Mitigation Measures
False negative or false positive results	Clinical performance testing, non-clinical performance testing, labeling
Use error / improper device use	Human factors assessment; labeling, including a description of user training
Device failure / malfunction	Non-clinical performance testing, labeling, software verification, validation, and hazard analysis
Electrical, thermal, mechanical, or light-related injury	Electrical, mechanical, and thermal safety testing, labeling, software verification, validation, and hazard analysis
Interference with other devices	Electromagnetic compatibility testing
Adverse tissue reaction	Biocompatibility evaluation, labeling
Infection and cross contamination	Sterilization validation, shelf-life testing, labeling

Specifically, in the proposed order published prior to the panel meeting, FDA proposed the following special controls:

(1) Clinical performance testing must demonstrate that the device improves assisted-read detection or diagnostic characterization of lesions suspicious for melanoma compared to characterization of lesions without the device in the indicated user population(s) when used in accordance with the instructions for use.

(2) Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. Such testing must include testing of safety features intended to mitigate device specific hazards and must demonstrate:

  (i) Electromagnetic compatibility, and electrical, mechanical, and thermal safety.

  (ii) Continued sterility and package integrity of components that must be sterile, as well as continued device functionality, over the identified shelf life of the device.

(3) Sterilization validation must be conducted for components that must be sterile.

(4) The elements of the device that may contact the patient must be demonstrated to be biocompatible.

(5) Software verification, validation, and hazard analysis must be performed.

(6) A human factors assessment must demonstrate that the intended user can correctly use the device according to the intended use following user training.

(7) Labeling must include:

  (i) A description of the device and information needed to facilitate clinical interpretation of all device outputs.

(ii) Information regarding the intended patient population and anatomical site(s), type(s) of lesions, compatible hardware, and compatible image acquisition parameters used with the device in order to achieve the intended use.

(iii) A summary of any clinical testing conducted to demonstrate how the device functions in providing information about the skin lesion. The summary must include the following:

(A) A description of each device output and clinical interpretation.

(B) Any performance measures, including sensitivity and specificity.

(C) Relevant characteristics of the patients studied in the clinical validation (including age, gender, race or ethnicity, disease category), inclusion and exclusion criteria, and a summary of validation results.

(D) The expected performance of the device for all intended use populations.

(iv) A statement that the device is not intended for use as a stand-alone diagnostic.

(v) User qualifications needed for safe use of the device, including a description of user training required prior to use, and a statement that the device is intended to be used by a dermatologist.

(vi) Warnings and cautions to mitigate any device specific hazards, including the following:

(A) Identifying foreseeable situations in which the device is likely to fail or not to operate at its expected performance level; and

(B) For devices that utilize energy to provide adjunctive diagnostic information, unless available information demonstrates that the specific warnings and cautions do not apply, a statement warning users about exclusion of lesions close to the eye and unsafe energy exposure to the eyes.

(vii) Instructions for device maintenance and validated methods and instructions for reprocessing of any reusable components.

8. Summary

The devices that are proposed to be reclassified as computer-aided devices which provide adjunctive diagnostic information about lesions suspicious for melanoma are currently classified in Class III, the most stringent regulatory category in the premarket review process. In light of the information available, the Panel will be asked to comment whether computer-aided devices which provide adjunctive diagnostic information about lesions suspicious for melanoma fulfill the statutory definition associated with a Class II (special controls) device designation. FDA believes that these devices may be more appropriately regulated as:

- Class II, meaning general and special controls are sufficient to provide reasonable assurance of its safety and effectiveness

  As opposed to:

- Class III, meaning the most stringent regulatory category for devices. Class III devices are typically high-risk devices and include devices for which insufficient information exists to provide reasonable assurance of safety and effectiveness solely through general or special controls.

FDA believes that special controls along with general controls will be adequate to ensure the safety and effectiveness of these devices. FDA is seeking the Panel's input regarding whether the available scientific evidence supports a Class II determination with appropriate special controls.

For the purposes of classification (refer to the Regulatory Reference Sheet for additional information), FDA considers the following items, among other relevant factors, as outlined in 21 CFR 860.7(b):

- The persons for whose use the device is represented or intended;
- The conditions of use for the device, including conditions of use prescribed, recommended, or suggested in the labeling or advertising of the device, and other intended conditions of use;
- The probable benefit to health from the use of the device weighed against any probable injury or illness from such use; and
- The reliability of the device.

Part (g)(1) of this regulation further states that "It is the responsibility of each manufacturer and importer of a device to assure that adequate, valid scientific evidence exists, and to furnish such evidence to the Food and Drug Administration to provide reasonable assurance that the device is safe and effective for its intended uses and conditions of use. The failure of a manufacturer or importer of a device to present to the Food and Drug Administration adequate, valid scientific evidence showing that there is **reasonable assurance of the safety and effectiveness** of the device, if regulated by general controls alone, or by general controls and special controls, may support a determination that the device be classified into class III."

8.1 Indications for Use

FDA believes that computer-aided devices which provide adjunctive diagnostic information about lesions suspicious for melanoma can provide useful diagnostic information before final biopsy decision. The devices can also provide dermatologists an additional source of adjunctive information when triaging patient care for melanoma. These devices are indicated for use by dermatologists on skin lesions suspicious for melanoma, not on lesions determined to be melanoma or other skin lesions.

8.2 Reasonable Assurance of Safety

According to 21 CFR 860.7(d)(1), "There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use."

In plain language, the definition states that a reasonable assurance of safety exists if, when using the device properly:
- The probable benefits to health outweigh the probable risks, and
- There is an absence of unreasonable risk of illness or injury

FDA has identified potential risks to health associated with computer-aided devices which provide adjunctive diagnostic information about lesions suspicious for melanoma, based on the public and non-public information (published literature, MDRs, recalls, and Summary of Safety and Effectiveness Data documents) available to FDA. The risks to health are discussed in Section 5 of this document.

FDA will ask the Panel whether the evidence demonstrates a reasonable assurance of safety for the indications for use described above.

8.3 Reasonable Assurance of Effectiveness

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

In plain language, the definition states that if using the device properly provides clinically significant results in a significant portion of the target population, there is a reasonable assurance of effectiveness.

FDA will ask the Panel whether there is a reasonable assurance of effectiveness for computer-aided devices which provide adjunctive diagnostic information about lesions suspicious for melanoma for the indications for use described above.

8.4 Special Controls

If the Panel were to recommend a Class II determination, FDA believes that the special controls proposed in Section 8, above, should be included as special controls. FDA proposes that special controls for computer-aided devices which provide adjunctive diagnostic information about lesions suspicious for melanoma devices would include both performance testing elements as well as labeling requirements.

The Panel will be asked whether the proposed special controls can adequately mitigate the risks to health for computer-aided devices which provide adjunctive diagnostic information about lesions suspicious for melanoma and provide a reasonable assurance of safety and effectiveness in light of the available scientific evidence.

8.5 Reclassification

As previously noted, FDA considers a device Class II when general and special controls are sufficient to provide reasonable assurance of its safety and effectiveness. In order to change the classification of computer-aided devices which provide adjunctive diagnostic information about lesions suspicious for melanoma from Class III to Class II, FDA must have sufficient information to establish special controls that can provide reasonable assurance of the safety and effectiveness that, when using the device properly:

- The probable benefits to health from using the device will outweigh the probable risks (per the definition of a reasonable assurance of safety, 21 CFR 860.7(d)(1))

- There is an absence of unreasonable risk of illness or injury (per the definition of a reasonable assurance of safety)

- The device will provide clinically significant results in a significant portion of the target population (per the definition of a reasonable assurance of effectiveness, 21 CFR 860.7(e)(1))

Special controls include "the promulgation of performance standards, post market surveillance, patient registries, development and dissemination of guidance documents (including guidance on the submission of clinical data in premarket notification submissions in accordance with section 510(k) of the FD&C Act), recommendations, and other appropriate actions as the Commissioner deems necessary to provide such assurance."

For computer-aided devices which provide adjunctive diagnostic information about lesions suspicious for melanoma, FDA believes that the available evidence suggests that special controls can be used to provide a reasonable assurance of safety and effectiveness.

Based on the available scientific evidence and proposed special controls, the Panel will be asked whether a Class II or a Class III designation is appropriate for computer-aided devices which provide adjunctive diagnostic information about lesions suspicious for melanoma.

9. Questions

1. FDA has identified the following risks to health for computer-aided devices which provide adjunctive diagnostic information to dermatologists about lesions suspicious for melanoma based on available information for these devices, including data in P090012 available to FDA under section 520(h)(4) of the FD&C Act, input from the 2010 Panel on P090012, published peer-reviewed literature, and postmarket experience associated with use of these devices:

- *False negative or false positive results* - False negative results could result in complications such as incorrect or delayed diagnoses and delays in biopsy decisions and melanoma treatment, which may allow an undetected condition to worsen and potentially increase morbidity and mortality. False positive results may result in complications such as incorrect management of the patient, including unnecessary additional invasive biopsy procedures and more frequent screenings, as well as the potential administration of inappropriate treatments and/or the withholding of appropriate treatments, with adverse effects.

- *Use error / improper device use* - The device could be misused to analyze images from an unintended patient population, an unintended anatomical site, or lesions having an unintended attribute, or to analyze images acquired with incompatible imaging hardware or incompatible image acquisition parameters, resulting in the device not operating at its expected performance level. The device could also be misused if the user does not follow the appropriate reading protocol for using the device to assess lesions of interest, which may lead to lower accuracy. Inaccurate results may result in the same complications associated with false negative or false positive results as discussed above.

- *Device failure / malfunction* - Device failure or malfunction could result in the absence or delay of device output, or incorrect device output, which could lead to inaccurate patient assessment. Inaccurate results may result in the same complications associated with false negative or false positive results as discussed above.

- *Electrical, thermal, mechanical, or light-related injury* – While in operation, the device may discharge electricity that could shock the user or patient. Electrical discharge or exposure to device-generated heat may cause thermal injury or discomfort. Moving parts may cause mechanical injury. For devices that utilize light to provide adjunctive diagnostic information, accidental eye exposure to the light source could cause eye injury.

- *Interference with other devices* – Individuals with electrically powered implants could experience an adverse interaction with the device due to electromagnetic interference or radiofrequency interference.

- *Adverse tissue reaction* - A patient could experience skin irritation and/or allergic reaction associated with the use and operation of the device via the use of non-biocompatible materials in patient-contacting devices.

- *Infection / cross contamination* – If certain components of the device are not adequately sterilized or if reusable components are not adequately reprocessed between uses, the device may introduce pathogenic organisms to patients and cause an infection.

a) **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.**

b) **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.**

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:

  o determine that general controls are sufficient to provide reasonable assurance of the safety and effectiveness, OR

  o 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.

a) **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:**

    i) **Prohibition against adulterated or misbranded devices,**
    ii) **Good Manufacturing Practices (GMP),**
    iii) **Registration of manufacturing facilities,**
    iv) **Listing of device types,**
    v) **Record keeping, etc.**

b) **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.**

c) **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.**

d) **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.**

3. 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.

10. References

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