All Too Wellness, LLC

DRAFT Consultant Report

AI Labs Group S.L.

DRAFT Strategy Report for Legit.Health Plus

2025-08-29

Prepared By:

Brendan O'Leary

Disclaimer

The conclusions and recommendations provided in this Consultant Report are based on our evaluation of the data, results and conclusions in the source documents provided by the client. We cannot confirm that all relevant documents or information were made available, and a complete, independent verification of the results and conclusions reported in the source documents provided was not conducted. The recommendations and opinions expressed herein are advisory in nature, and the client retains all responsibility for any use or implementation.

This page is intentionally left blank.

Contents

Executive summary **3**

1 Report objectives **4**

2 Major functionality of the Legit.Health Plus device **4**

3 History of Skin Lesion Analyzer (SLA) regulation in the United States **7**

3.1 The FDA approves two devices through the PMA pathway 7

3.2 The FDA convenes a panel and considers reclassification 8

3.3 The FDA grants a De Novo 9

4 Proposed draft indications for use **10**

4.1 Option 1: SLA for PCPs: Evaluate skin lesions suggestive of melanoma, basal cell carcinoma, and/or squamous cell carcinoma 10

4.2 Option 2: SLA for PCPs: Evaluate skin lesions not suggestive of melanoma, basal cell carcinoma, and/or squamous cell carcinoma 11

4.3 Option 3: SLA for lay persons 11

4.4 Option 4: SLA for Dermatologists 11

5 Regulatory pathway **11**

6 Necessary studies **11**

7 Conclusion **11**

Appendices **12**

A How the FDA regulates medical devices **12**

A.1 Medical device types and classifications 12

A.2 General controls: Requirements for almost all medical devices 12

A.3 Special controls: Additional requirements for particular types of medical devices 14

A.4 Additional considerations for software 14

A.4.1 Software As a Medical Device (SaMD), the Pre-Cert pilot, and device software functions (DSFs) 14

A.4.2 Machine Learning (ML) . . . 15
A.4.3 Cybersecurity . . . 16
A.5 Interactions with the FDA during medical device development . . . 16
A.5.1 Investigational devices . . . 16
A.5.2 Breakthrough devices . . . 17
A.5.3 Presubmissions . . . 17
A.6 The FDA's most frequently used pathways to market . . . 18
A.6.1 Exempt devices . . . 18
A.6.2 The 510(k) pathway . . . 19
A.6.3 The De Novo pathway . . . 19
A.6.4 The premarket approval (PMA) pathway . . . 20

B Relevant FDA device classification regulations and precedents 22

B.1 § 878.1830: Software-aided adjunctive diagnostic device for use by physicians on lesions suspicious for skin cancer . . . 22
B.2 PMA devices . . . 24

C Common acronyms and abbreviations 26

List of Tables

1 Product codes associated with 21 CFR 878.1830 for "Software-aided adjunctive diagnostic device for use by physicians on lesions suspicious for skin cancer." 23
2 Most recent FDA-authorized devices: "Software-Aided Adjunctive Diagnostic Device For Use By Physicians On Lesions Suspicious For Skin Cancer" . . . 23
3 Product codes associated with PMA SLAs. . . . 24
4 Most recent FDA-authorized devices: PMA SLAs. . . . 24
5 Acronyms and Abbreviations . . . 26

List of Figures

1 SLA Workflow . . . 10

Executive summary

(TODO)

1 Report objectives

(TODO)

2 Major functionality of the Legit.Health Plus device

Legit.Health describes the Legit.Health Plus device as including algorithms related to:

1. ICD category distribution (the "top-5 function"): "The system highlights the top five ICD-11 disease categories, each accompanied by its corresponding code and confidence score, thereby supporting clinicians with both ranking and probability information. . ."[1]

   Legit.Health proposes to assess the accuracy of this function using "Top-k Accuracy" to a reference standard based on "expert" annotations of images. This measure is related to sensitivity or positive percent agreement (PPA). Legit.Health proposes performance targets of:

   - Lower bound of the 95% confidence interval for top-1 accuracy $\geq 55\%$
   - Lower bound of the 95% confidence interval for top-3 accuracy $\geq 70\%$
   - Lower bound of the 95% confidence interval for top-5 accuracy $\geq 80\%$

   No performance metrics related to specificity, or negative percent agreement (NPA), are proposed, nor are measures related to predictive value (i.e., positive predictive value (PPV) and negative predictive value (NPV)).

2. Binary indicators (the "malignancy indicator function"): "Each indicator reflects the aggregated probability that a case belongs to clinically meaningful categories requiring differential triage or diagnostic attention."[2]

   1. **Malignant**: probability that the lesion is a confirmed malignancy (e.g., melanoma, squamous cell carcinoma, basal cell carcinoma).
   2. **Pre-malignant**: probability of conditions with malignant potential (e.g., actinic keratosis, Bowen's disease).
   3. **Associated with malignancy**: benign or inflammatory conditions with frequent overlap or mimicry of malignant presentations (e.g., atypical nevi, pigmented seborrheic keratoses).
   4. **Pigmented lesion**: probability that the lesion belongs to the pigmented subgroup, important for melanoma risk assessment.
   5. **Urgent referral**: lesions likely requiring dermatological evaluation within 48 hours (e.g., suspected melanoma, rapidly growing nodular lesions, bleeding or ulcerated malignancies).

[1] See: "R-TF-028-001 AI/ML Description" (dated 2025-08-22), p. 1.
[2] See: "R-TF-028-001 AI/ML Description" (dated 2025-08-22), p. 2.

6. **High-priority referral**: lesions that should be seen within 2 weeks according to dermatology referral guidelines (e.g., suspected non-melanoma skin cancer, premalignant lesions with malignant potential).[3]

Legit.Health proposes to assess the accuracy of these functions using the area under the receiver operating characteristics curve (AUC or AUROC) with a performance target of the lower bound of the 95% confidence interval for AUC ≥ 0.80 against a reference standard of "dermatologist" consensus image labels for each classifier.

3. Erythema intensity quantification (the "erythema severity function"): A function with semi-quantitative output (10 ordinal categories) related to the severity of erythema (redness caused by increased blood flow).[4]

   Legit.Health proposes to assess the accuracy of this functions using the Relative Mean Absolute Error (RMAE) with a performance target of the upper bound of the 95% confidence interval for RMAE $\leq$ 20% against a reference standard of "multi-expert" image labels.

4. Desquamation intensity quantification (the "desquamation severity function"): A function with semi-quantitative output (10 ordinal categories) related to the severity of desquamation (peeling skin).[5]

   Legit.Health proposes to assess the accuracy of this functions using the RMAE with a performance target of the upper bound of the 95% confidence interval for RMAE $\leq$ 20% against a reference standard of "multi-expert" image labels.

5. Nodule quantification (the "nodule detection and counting function"): "A deep learning **object detection model** ingests a clinical image and outputs bounding boxes with associated confidence scores for each detected nodule."[6] As a post-processing step, a count of nodules is produced, and this serves as the ultimate output of the function.

   Legit.Health proposes to assess the accuracy of this functions using the Mean Absolute Error (MAE) with a performance target of the upper bound of the 95% confidence interval for MAE $\leq$ "Expert Inter-observer Variability" against a reference standard of "expert" counts of nodules present in images.

   In addition, for underlying object detection, Legit.Health proposes to assess a "Deviation" metric ($\leq$ 10% of inter-observer variance)[7] and will report precision (PPV), recall (PPA), and F1-score.

   It is not clear how or if measures of performance on images with no nodules present will be assessed (e.g., image-level NPA).

6. Hair loss surface quantification (the "hair loss quantification function"): "A deep learning segmentation model ingests a clinical image of the scalp and outputs a three-class

[3] See: "R-TF-028-001 AI/ML Description" (dated 2025-08-22), p. 2.
[4] See: "R-TF-028-001 AI/ML Description" (dated 2025-08-22), p. 3.
[5] See: "R-TF-028-001 AI/ML Description" (dated 2025-08-22), p. 4.
[6] See: "R-TF-028-001 AI/ML Description" (dated 2025-08-22), p. 5.
[7] TODO: I do not understand, precisely, what is being proposed here.

probability map for each pixel."[8] The classes are "hair," "no hair," and "non-scalp." The output is a percentage of hair loss surface area, a measure of the extent of alopecia (hair loss).

Legit.Health proposes to assess the accuracy of the non-scalp classifier using the Intersection over Union (IoU), with a lower bound of the 95% confidence interval for IoU ≥ 0.50 compared to "expert" annotations.

For percentage hair loss, Legit.Health proposes to assess accuracy using Relative Error (RE%), with an upper bound of the 95% confidence interval for RE $\leq 20\%$ compared to "expert" annotations.

This is a complex portfolio of functions, with each function raising its own scientific evaluation and regulatory considerations. For example, some aspects of the malignancy indicator function are similar to skin lesion analyzers (SLAs) the FDA has previously regulated (see Section 3, "History of Skin Lesion Analyzer (SLA) regulation in the United States," beginning on page 7). The nodule detection and counting function may be similar in some regards to computer aided detection (CADe) and diagnosis (CADx) devices used for lung cancer. The segmentation and intensity functions (the erythema severity function, the desquamation severity function, and the hair loss quantification function) may have some similarities to technologies used to analyze digital pathology slides for prostate cancer or images from colonoscopies. At this time, I am not aware of any precedent for providing output like the output that is proposed for the top-5 function.

Furthermore, it is not clear whether or how these functions are assembled into one product or workflow. For example, it does not appear to make sense to route a single image to both the nodule detection and counting function and the hair loss quantification function. Therefore, the nodule detection and counting function and the hair loss quantification function are probably best considered as independent medical devices with independent regulatory strategies. The same may be true for the erythema severity function and the desquamation severity function. Legit.Health may be able to significantly de-risk the regulatory process by separating the functions as much as possible so that Legit.Health can have the option to develop, study, and submit each function to the FDA separately, either sequentially or in parallel.

With that in mind, this report will prioritize considerations related to the top-5 function and the malignancy indicator function, which, together, would form the initial minimum viable product (MVP) for a US launch. For the purposes of this report, "Legit.Health Plus" refers to a device comprising some form of these two functions.

[8] See: "R-TF-028-001 AI/ML Description" (dated 2025-08-22), p. 7.

3 History of Skin Lesion Analyzer (SLA) regulation in the United States

3.1 The FDA approves two devices through the PMA pathway

2011-11-01: The FDA approves P090012[9] for the MELA Sciences, Inc. MelaFind device. The device has the following indications for 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., non-ulcerated 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.

This device includes custom hardware and computer vision software. A post-approval study was required. Various minor updates have since been approved under PMA supplements, with the most recent on 2016-08-18 (P090012/S011). Product code OYD was established as a result of the original approval for the MelaFind device, and no other device has been authorized under this product code.

[9] SSED: https://www.accessdata.fda.gov/cdrh_docs/pdf9/P090012B.pdf.

2017-06-28: The FDA approves P150046[10] for the SciBase AB Nevisense device. The device has the following indications for 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 Nevisense 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).

This device includes custom hardware to measure electrical impedance. A post-approval study was not required. Various minor updates have since been approved under PMA supplements, with the most recent on 2020-04-30 (P150046/S004). Product code OVN was established as a result of the original approval for the Nevisense device, and no other device has been authorized under this product code.

3.2 The FDA convenes a panel and considers reclassification

2022-05-27: The FDA announces that it will have a panel meeting to discuss the necessary studies and regulatory approach for skin lesion analyzers. [1]

2022-06-30: The FDA issues a proposed rule that, if finalized, would "reclassify optical diagnostic devices for melanoma detection and electrical impedance spectrometers, both of which are postamendments class III devices (product codes OYD and ONV, respectively), into class II (special controls), subject to premarket notification." [2] This rule would move these devices from the PMA pathway to the 510(k) pathway. (See: Appendix A.6.4, "The

[10] SSED: https://www.accessdata.fda.gov/cdrh_docs/pdf15/P150046B.pdf.

premarket approval (PMA) pathway," beginning on page 20 and Appendix A.6.2, "The 510(k) pathway," beginning on page 19.) As of this report, this rule has not been finalized.

2022-07-28 through 2022-07-30: The FDA convenes the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee to discuss the scientific considerations underpinning the review of these devices and the proposed rule.

See:

- The FDA's executive summary, which provides background information for panel members in advance of the meeting.
- The FDA's presentation.
- Day 1 video, summary minutes, and transcript.
- Day 2 video[11], summary minutes and transcript.
- The FDA's 24h summary, which provides a quick summary of what was covered in the meeting.

3.3 The FDA grants a De Novo

2024-01-12: The FDA grants DEN230008[12], Dermasensor Inc.'s De Novo reclassification petition for the DermaSensor device. The device has the following indications for use:

> The DermaSensor device is indicated for use to evaluate skin lesions suggestive of melanoma, basal cell carcinoma, and/or squamous cell carcinoma in patients aged 40 and above to assist in the decision regarding referral of the patient to a dermatologist. The DermaSensor device should be used in conjunction with the totality of clinically relevant information from the clinical assessment, including visual analysis of the lesion, by physicians who are not dermatologists. The device should be used on lesions already assessed as suspicious for skin cancer and not as a screening tool. The device should not be used as the sole diagnostic criterion nor to confirm clinical diagnosis of skin cancer.

Postmarket data collection and surveillance was required by a special control. The FDA established a new regulation, 21 CFR 878.1830 (see Appendix B.1, "§ 878.1830: Software-aided adjunctive diagnostic device for use by physicians on lesions suspicious for skin cancer," beginning on page 22), by granting this De Novo. While this regulation is final and is in effect, this regulation is not yet published in the Code of Federal Regulations (CFR) and may not be easy to find online. Product code QZS was established as a result of the original authorization for the DermaSensor device, and no other device has been authorized under this product code (see Table 2 on page 23).

[11] This video is currently private on YouTube and cannot be accessed.
[12] Decision summary: https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN230008.pdf.

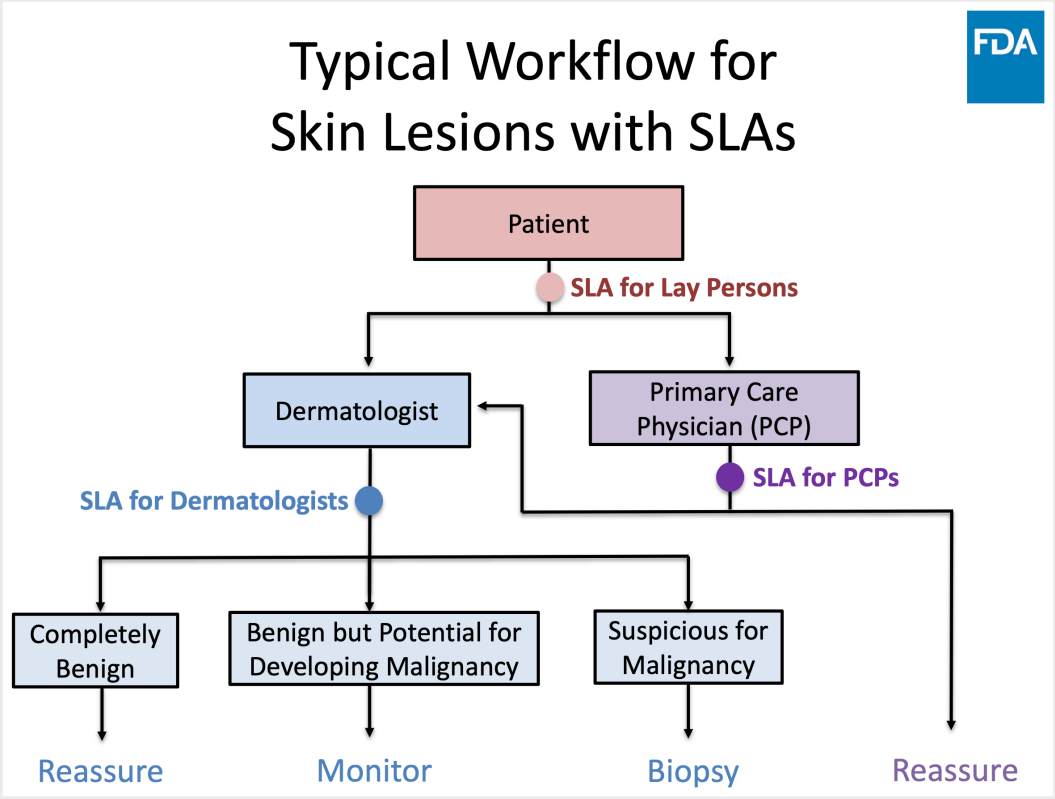

Figure 1: The FDA's illustration of SLA workflows at the 2022-07-28 panel meeting. See: https://www.fda.gov/media/160760/download. While SLAs for Dermatologists were not reclassified and remain PMA devices, certain SLAs for PCPs were placed in Class II (510(k)) via the DermaSensor De Novo. As of this report, there are no legally marketed SLAs for Lay Persons in the United States.

The most notable difference between this device and the previous devices that went through the PMA pathway appears to be the intended user. The PMA devices are intended for use by dermatologists ("SLA for Dermatologists"). This device is intended for use by physicians who are not dermatologists ("SLA for PCPs"). See Figure 1.

4 Proposed draft indications for use

4.1 Option 1: SLA for PCPs: Evaluate skin lesions suggestive of melanoma, basal cell carcinoma, and/or squamous cell carcinoma

(TODO: Likely 510(k). Sensitivity (positive percent agreement) must exceed 90%. Predicate is DermaSensor.)

4.2 Option 2: SLA for PCPs: Evaluate skin lesions not suggestive of melanoma, basal cell carcinoma, and/or squamous cell carcinoma

(TODO: Very unclear regulatory path. FDA could require a De Novo or could clear this through 510(k). We would propose that the predicate be DermaSensor.)

4.3 Option 3: SLA for lay persons

(TODO: Likely De Novo, but FDA could require a PMA.)

4.4 Option 4: SLA for Dermatologists

(TODO: Likely PMA.)

5 Regulatory pathway

(TODO – I think 510(k) or De Novo as long as it is not indicated for dermatologists.)

6 Necessary studies

(TODO – see special controls in Appendix B.1, "§ 878.1830: Software-aided adjunctive diagnostic device for use by physicians on lesions suspicious for skin cancer," beginning on page 22. Need to decide on indications before investing in this section.)

7 Conclusion

(TODO)

Appendices

A How the FDA regulates medical devices

A.1 Medical device types and classifications

The FDA groups medical devices into "classification regulations" and "product codes" based on each device's intended use and technological characteristics. These groups may also be called "device types." The FDA has "classified" device types into one of three categories based on risk: Class I (lower risk), Class II (moderate risk), and Class III (higher risk). The FDA applies regulatory requirements to device types according to their risk. While there are exceptions, it usually works out like this:

- **Class I**: Lower risk devices are subject to **general controls** but are exempt from premarket review.
- **Class II**: Moderate risk devices are subject to **general controls** and premarket review through the **510(k)** pathway. In some cases, they are also subject to **special controls**.
- **Class III**: Higher risk devices are subject to **general controls** and premarket review through the **premarket approval (PMA)** pathway. They are also subject to other requirements associated with the PMA pathway, including pre-approval inspections, annual reports, and more.

In a general sense, the overarching goal of the framework is to subject devices to the regulatory controls necessary to provide a "reasonable assurance of safety and effectiveness" based on their benefits and risks.

If a novel type of medical device is invented for which there is no existing classification regulation, it is, by default, in Class III, meaning that a PMA submission is required. However, if the developer of that device believes that "general controls or general and special controls would provide reasonable assurance of the safety and effectiveness of the device", they can request classification into Class I or Class II through the **De Novo** premarket pathway. [3, p. 7] If the FDA grants the De Novo classification request, the device can proceed to market and similar devices, whether from the same developer or from other developers, can follow the device to market through the 510(k) pathway. This is discussed in more detail in Section A.6, "The FDA's most frequently used pathways to market," beginning on page 18.

A.2 General controls: Requirements for almost all medical devices

General controls typically apply to all medical devices and are described in some depth on the FDA's website.[13] They require that a medical device be free of adulteration and misbranding. A medical device is adulterated if, for example, it is unsanitary, fails to meet

[13] See: https://www.fda.gov/medical-devices/regulatory-controls/general-controls-medical-devices.

an applicable performance standard, is not PMA approved when that is required, or is in violation of good manufacturing practices. A medical device is misbranded if, for example, its labeling is false or misleading, it is missing required labeling, or, if it is an over-the-counter (OTC) device, it is not provided with adequate instructions for use.

In addition, general controls require that medical device manufacturers, including medical device software developers, register the physical facilities they use to manufacture and distribute their devices and list the devices associated with those facilities. This is called "Registering and Listing." This makes it possible for the FDA to locate these facilities and, occasionally, inspect them.[14]

General controls also include a requirement to notify the FDA before bringing new devices to the market (see Section A.6.2, "The 510(k) pathway," beginning on page 19), unless the device type is exempt (see Section A.6.1, "Exempt devices," beginning on page 18).

General controls also require that devices be manufactured in accordance with "Current Good Manufacturing Practices" (CGMPs), which are governed by the "Quality System Regulation" (QSR). Implementing a quality system that meets the FDA's requirements is a major undertaking. In practice, the quality system should be developed in accordance with ISO 13485:2016 [4], as the FDA recently finalized a rule that will replace the existing QSR with this standard in 2026.[15] If you plan to implement a quality system for your product in the future, start by documenting your design decisions now. This includes writing well-specified product requirements against which you can verify and validate your product in the future. [5]

Although not strictly a general control, medical device manufacturers are also required to report device-related adverse events and product problems to the FDA.[16] Depending on the nature of the event, the FDA must be notified within either 5 working days or 30 calendar days. In addition, medical device manufacturers must establish "complaint handling" procedures and must evaluate complaints to determine if they must be reported to the FDA as adverse events.

Establishing and maintaining the systems and processes necessary to develop, manufacture, and market a medical device, including a software medical device, under general controls is a major undertaking.

[14] Sometimes, you will come across an advertisement for a medical device that says that the device is "registered" or "listed" with the FDA. This typically means that the manufacturer paid a fee, entered an address into a FDA database, and told the FDA that they were making the device at that address. It does not mean that any real person at the FDA has ever applied any scrutiny whatsoever to the device or the manufacturer. That is: it does not mean much at all.

[15] See: https://www.fda.gov/medical-devices/postmarket-requirements-devices/quality-system-qs-regulationmedical-device-current-good-manufacturing-practices-cgmp.

[16] See: 21 CFR Part 803.

A.3 Special controls: Additional requirements for particular types of medical devices

For Class II device types, the FDA has the authority to establish special controls in addition to general controls to provide a reasonable assurance of safety and effectiveness. Special controls can cover a range of topics, from interoperability, to special labeling requirements, or requirements to conduct certain clinical studies. Although these requirements can be established at any time by issuing new regulations, they are more commonly established through the De Novo process (see Section A.6.3, "The De Novo pathway," beginning on page 19). When established through this process, special controls are proposed by the developer of the novel device being reviewed in the De Novo. Nonetheless, the FDA has the final word on what special controls will be applied to a new type of medical device established through the De Novo process.[17]

A.4 Additional considerations for software

Although software has been regulated under the medical device regulatory framework since it was established in 1976, the framework is, in many key ways, oriented towards the regulation of hardware medical devices, like surgical equipment, radiology machines, diagnostic tests, and similar technologies. The FDA has increasingly sought to better translate or tailor the framework to software over time.

A.4.1 Software As a Medical Device (SaMD), the Pre-Cert pilot, and device software functions (DSFs)

International regulators, including the FDA, have defined Software as a Medical Device, or SaMD, as "software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device," which means that the software must not be necessary for the hardware medical device to achieve its intended medical purpose and that the software is not intended to "drive," or control, a hardware medical device. [6, p. 6]

Under this definition, because SaMD does not control physical actuators, SaMD typically does not pose a risk of direct physical harm to users and patients. Instead, the risk of SaMD is linked to the quality and reliability of the information the software is providing to users.

The FDA sought to establish a distinct regulatory pathway for SaMD through the "Software Precertification (Pre-Cert) Pilot Program." [7] The goal of this pilot was to explore whether the FDA could assure the safety and effectiveness of medical device software by focusing its oversight on ensuring that development organizations had established a "Culture of Quality

[17] Unlike other rules, special controls established through the De Novo process are the result of an "administrative order." This means they do not go through the standard rule-making process: There is no economic analysis, and there is no public comment period. This makes the De Novo process an unusually fast and powerful regulatory tool for the FDA, but it can still feel very slow for developers from other industries. See Section A.6.3, "The De Novo pathway," beginning on page 19, for an overview of the time required.

and Organizational Excellence (CQOE)." Such developers could then market medical device software without further review.

In principle, the concept has structural similarities to the current framework for lower risk "Exempt" devices (see Section A.6.1, "Exempt devices," beginning on page 18), with a CQOE occupying a similar role to that of a Quality System in the traditional model. Along these lines, the FDA noted in its final report on the pilot program that "further development is needed before being able to identify low-risk devices where an organizational appraisal alone could be relied upon without further premarket review of the device," and "organizational appraisals would not be sufficient to take the place of device-specific clinical performance reviews and cybersecurity reviews for all moderate-risk devices, and device-specific reviews of these elements are of particular value for higher-risk and novel devices." [7, p. 12] Products included in the pilot went through the traditional framework concurrently, and the FDA found that a new law would be needed to implement a program like the Pre-Cert pilot for SaMD in place of the traditional framework.

As the Pre-Cert pilot was underway, the FDA also explored regulatory approaches for medical devices enabled by Artificial Intelligence (AI) and Machine Learning (ML) (see Section Section A.4.2, "Machine Learning (ML)," beginning on page 15). In the course of this work and in the course of implementing the software provisions of the Cures Act, the FDA increasingly moved away from the term SaMD in key documents. Instead, the broader term "device software functions" (DSF), which includes SaMD and software functions that are not SaMD, was used. Proposed frameworks that were originally scoped to apply only to SaMD were expanded to include software functions that were necessary for a hardware medical device to achieve its intended medical purpose and software functions that control hardware medical devices. This may have reflected a recognition by the FDA that there is lower risk software that is not SaMD and that the concepts being proposed for SaMD may have applicability for other software as well.

Although work on SaMD-specific approaches is continuing,[18] today, the FDA does not have or implement a separate regulatory framework for SaMD. Instead, SaMD is regulated under the FDA's regulatory framework for all medical devices. The U.S. Congress would likely need to pass a new law for this to change.

A.4.2 Machine Learning (ML)

The FDA and international regulators issued Guiding Principles on Good Machine Learning Practice for Medical Device Development in 2021. [8] This language parallels language used to describe current good manufacturing practices (CGMPs), but it does not reflect a final policy or regulation from the FDA. Later, in 2023, the FDA and international regulators issued Guiding Principles on Predetermined Change Control Plans for Machine Learning-Enabled Medical Devices. [9] This followed a draft guidance from the FDA on the same topic earlier that year. [10]

[18] See, for example, the International Medical Device Regulator's Forum (IMDRF) working group: https://www.imdrf.org/working-groups/software-medical-device.

These approaches are based on the FDA's experience authorizing several hundred AI or ML-enabled medical devices for marketing in the United States.[19]

The FDA has substantial experience with AI and ML-enabled devices, particularly for imaging, and the FDA has shown a clear willingness to pursue new approaches, such as predetermined change control plans (PCCPs) that enable these devices to be updated without additional review by the FDA provided that robust procedures are in place to study and monitor the performance of the technology over time or to evaluate new versions of models before they are deployed.

A.4.3 Cybersecurity

The FDA is continuing to make extensive updates to its approach to medical device cybersecurity. [11] [12] [13] Although a detailed description of the relevant requirements is beyond the scope of this document, it is important to ensure that adequate cybersecurity expertise is present on the device design team early in the development process, and the FDA will scrutinize cybersecurity documentation closely in the premarket review process for medical devices, in addition to more traditional medical device software documentation. [14]

A.5 Interactions with the FDA during medical device development

A.5.1 Investigational devices

Before a medical device reaches the market through a premarket pathway, such as the 510(k) or De Novo pathway, it is often necessary to study the device to gather evidence of its safety and effectiveness for its intended use. Devices can be studied before they are authorized by the FDA under an "Investigational Device Exemption" (IDE), a process through which the FDA and/or an Institutional Review Board (IRB) ensures the protection of human subjects. In some cases, a study may be "exempt" from the FDA's IDE regulations. (This is a different sort of exemption than the 510(k) exemption described in Section A.6.1 beginning on page 18.) Otherwise, unless a device or a study poses a significant risk – the "potential for serious risk to the health, safety, or welfare of a subject" – the study can be overseen by an IRB. [15, p. 3] These studies follow "abbreviated requirements."[20] Studies that pose a significant risk are subject to additional requirements, and the FDA itself must approve the study before it can begin.

Once they get to the FDA, IDEs are approved, approved with conditions, or disapproved within 30 days. They typically range from several dozen to several hundred pages in length.

[19] See: https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-aiml-enabled-medical-devices.

[20] See: 21 CFR 812.2(b).

A.5.2 Breakthrough devices

Depending on the quality of early evidence for a proposed product, FDA may grant a breakthrough device designation. [16] A variety of considerations, including resource constraints, play a role in determining whether a product will be accepted into the Breakthrough Device Program, including whether that product is already supported by some evidence that it may present a meaningful benefit to patients above and beyond what is currently available. [16, p. 9] Breakthrough designation prioritizes a product at the FDA as it goes through any of the pathways described above and may have downstream benefits with respect to coverage under "Transitional Coverage of Emerging Technology" (TCET). This should be considered when deciding what indications to pursue and what evidence to present to the FDA early in the course of interactions with the FDA.

For companies that are positioning themselves as acquisition targets for established medical device manufacturers, a breakthrough device designation can be a strong value signal to potential acquirers. In considering this strategy, it is important to note that the FDA has significant discretion about what devices it includes in the Breakthrough Program, and the FDA, due in part to resource constraints, has been increasingly conservative in granting breakthrough device designations.

A breakthrough device is one that meets the criteria below:

- First Criterion: The device provides for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions; and
- Second Criterion: Any one of the following:
  - The device represents breakthrough technology; or
  - The device has no approved or cleared alternatives; or
  - The device offers significant advantages over existing approved or cleared alternatives; or
  - Availability of the device is in the best interest of patients.

Notably, the FDA evaluates preliminary performance information when assessing the first criterion, so a breakthrough designation request involves providing some data to the FDA.

A.5.3 Presubmissions

A presubmission is a voluntary request for feedback from the FDA on specific topics and questions posed by a device developer to inform a future marketing submission. [17, p. 3] The FDA typically provides written feedback in response to these requests in approximately 70 days, with a 1-hour meeting, in person or virtual, about 5 days thereafter. [17, p. 20] Meeting minutes are finalized a few weeks later, depending on the speed of the device developer, who is responsible for drafting the minutes. Virtual meetings are typically easier to schedule.

A valuable use of the presubmission program is to obtain the FDA's feedback on a study design before the study starts. Product development time frames and estimates should account for the possibility that a follow-up meeting will be necessary if there is significant feedback on study design. To minimize the likelihood that the FDA will request follow-up meetings, it is important to prioritize requests for feedback and keep the number of topics discussed to a minimum.

A presubmission request can also specify that written feedback alone is sufficient and no meeting is needed. This can expedite simple interactions because it is not necessary to find a mutually agreeable time to meet, but the FDA's goal is still to provide written feedback in response to these requests in approximately 70 days. So, usually, it is better to request a meeting rather than written feedback alone. You can cancel the meeting if the written feedback turns out to be sufficient.

Presubmissions are part of a broader program called the "Q-submission" program. Many interactions with the FDA fall under this program, and there are arcane conventions around how they are tracked and what they are called. These details are outlined at some length in the FDA's policy for the program. [17]

Beyond a general awareness that the Q-submission program and the presubmission program within it cover many types of interactions with the FDA, for the purposes of this report, what is important to know is:

- You have opportunities to get the FDA's feedback as you develop your medical device.
- The FDA takes several months (usually about 70 days) to thoroughly consider the issues raised before providing that feedback.
- To make the most of each opportunity, it's important to provide a well-considered proposal for the FDA to react to, and it's important to prioritize your requests for feedback so the most important issues can be fully addressed.

A.6 The FDA's most frequently used pathways to market

A.6.1 Exempt devices

In the context of medical device regulatory requirements, "exempt" is usually a reference to well established lower risk device types for which premarket review by the FDA is not required, meaning that 510(k)s, De Novos, and PMAs are not required for these devices. While not reviewed by the FDA, exempt devices are typically subject to other requirements, including other general controls (see Section A.2, "General controls: Requirements for almost all medical devices," beginning on page 12). Sometimes, a substantial change to the intended use or technology used in an otherwise exempt device results in the device "tripping the limitations of the exemption." When the limitations of the exemption are tripped, premarket review by the FDA is required. Otherwise, the exempt pathway is the lowest burden path to market for FDA-regulated medical devices. This pathway is not available for novel device types.

A.6.2 The 510(k) pathway

The 510(k), or premarket notification, pathway is the most common path to market for medical devices that are not exempt from premarket review by the FDA. A successful 510(k) results in a determination by the FDA that a device is "substantially equivalent," or "SE" to a legally marketed predicate device with the same intended use and "clearance" to market the device. In the simplest but least common case, a device can be found to have the same technological characteristics (i.e. design, materials, energy source, or other characteristics) as a predicate device with the same intended use. This is rare: a device is usually not similar enough to a predicate device to support this type of determination. More commonly, a device can be found to have differences in technological characteristics that are not significant enough to raise different questions of safety and effectiveness than a predicate device with the same intended use. If this is the case, the new device can be shown, provided there is data to support this, to be as safe and effective as that predicate device and can therefore be found "substantially equivalent" to that predicate device. [18]

Devices that cannot be found SE to a predicate device are said to be "not substantially equivalent" (NSE). If a product would be found NSE because of a difference in its intended use or because differences in its technological characteristics raise different questions of safety or effectiveness than legally marketed devices, it is said to lack a predicate, and it is not eligible for the 510(k) pathway. In these cases, provided it is a lower or moderate risk device, a De Novo is typically the best option. If a device would be found NSE only because the data provided are insufficient to demonstrate that it is as safe and effective as a predicate device, the product remains eligible for the 510(k) pathway and may be found SE in the future with additional data or improvements. Additional information is available in guidance from the FDA, and the FDA provides a flowchart outlining the 510(k) decision making process in Appendix A of that guidance. [18, p. 27]

Although the process can take longer, device developers seeking a 510(k) should generally plan for the process to take up to 270 days from the date they provide a complete submission to the FDA (up to 90 days for the FDA to complete its review, and up to 180 days for the developer to answer questions if the FDA pauses its review to request additional information). [19] These submissions require extensive documentation, and it is not unusual for them to exceed one-thousand pages. [20]

A.6.3 The De Novo pathway

Under the FD&C Act, novel devices that cannot be found SE to a legally marketed predicate device through the 510(k) pathway are automatically subjected to the FDA's most stringent requirements (called "class III," requiring "premarket approval" or "PMA" submissions). In practice, this is not necessary for all novel technologies, and so the De Novo program was established to provide a more streamlined path to market for novel moderate risk technologies that lack a predicate. [3]

In a De Novo, the FDA makes a standalone assessment of the safety and effectiveness of the device under review. This includes reviewing proposed "special controls," a form of specific

regulatory requirement that is tailored to the new device type. When granting a De Novo, the FDA finalizes special controls that, when combined with general controls (requirements like the Quality Systems Regulation (QSR) and 510(k)), provide a "reasonable assurance of safety and effectiveness" for the device that was the subject of the De Novo and follow-on devices.

If a De Novo request is granted, future modifications to the device can be submitted as 510(k)s, and products from other manufacturers can also be brought to market through the 510(k) pathway by demonstrating substantial equivalence to the De Novo device and by meeting the applicable special controls. It is generally accepted that the "reasonable assurance of safety and effectiveness" review standard, which is used in both the De Novo and PMA marketing application pathways, is a more stringent standard than "substantial equivalence" and is more difficult to achieve, and this deters many developers from pursuing the De Novo pathway. That said, in my opinion based on my 14 years of experience at the FDA, the safety and effectiveness standard for 510(k), in its modern implementation for device types recently established through the De Novo process, is often not, in practice, lower than that for De Novo, and similar studies are often needed to support a positive decision from the FDA for similar indications for use under either pathway.

Additional information is available in guidance from the FDA, and the FDA provides a flowchart outlining the De Novo decision making process in Attachment 1 of the guidance. [3, p. 14]

Although the process can take longer, device developers seeking a De Novo should generally plan for the process to take up to 330 days from the date they provide a complete submission to the FDA (up to 150 days for the FDA to complete its review, and up to 180 days for the developer to answer questions if the FDA pauses its review to request additional information). [21] Like 510(k)s, these submissions require extensive documentation, and it is not unusual for them to exceed one-thousand pages.

A.6.4 The premarket approval (PMA) pathway

The premarket approval (PMA) pathway is the FDA's most stringent premarket pathway for medical devices. While this is the default pathway for novel devices for which a device type has not otherwise been classified (see Section A.1, "Medical device types and classifications," beginning on page 12), it is designed for higher risk devices that are "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... [present] a potential unreasonable risk of illness or injury."[21] In a PMA, a device developer must show that "there is reasonable assurance that the device is safe and effective for its conditions of use."[22] The FDA may also request input from a panel of outside experts in the course of a PMA review.[23] Manufacturers of PMA devices are inspected by the FDA before approval to ensure compliance with general controls, including the QSR (see Section A.2, "General

[21] 21 USC § 360c
[22] See: 21 CFR 860.7(c)(1).
[23] See: 21 CFR 814.44.

controls: Requirements for almost all medical devices," beginning on page 12). An additional inspection may occur approximately 1-year after approval.

If a PMA device is approved, further modifications are burdensome, and the FDA's policy on which of seven different PMA submission types to choose from when making various types of modifications extends to nearly 30 pages. [22] PMA devices are also subject to annual reporting requirements, and the FDA sometimes requires additional studies after the devices are approved.

The PMA pathway is the device review pathway that most resembles the pathway the FDA uses to approve new drugs. Given the difficulty and expense involved, it is not uncommon for a device developer to abandon a project if the FDA determines that a De Novo would be insufficient and that a PMA will be required.

Additional information is available in regulations and guidance documents from the FDA, and the FDA maintains a webpage that provides an overview of the pathway.[24]

Although the process can take longer, device developers seeking a PMA should generally plan for the process to take up to 360 days from the date they provide a complete submission to the FDA (up to 180 days for the FDA to complete its review, and up to 180 days for the developer to answer questions if the FDA pauses its review to request additional information). For PMAs that go to panel, the process can take up to 500 days (up to 320 days for the FDA to complete its review, and up to 180 days for the developer to answer questions if the FDA pauses its review to request additional information). [23] These submissions require extensive documentation, and it is not unusual for them to exceed several thousand pages.

[24] See: https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/premarket-approval-pma.

B Relevant FDA device classification regulations and precedents

B.1 § 878.1830: Software-aided adjunctive diagnostic device for use by physicians on lesions suspicious for skin cancer

While currently unpublished, this regulation was established by the DermaSensor De Novo and is likely to read as follows:

(a) **Identification**. A software-aided adjunctive diagnostic device for use by physicians on lesions suspicious for skin cancer is a prescription device that uses a software algorithm to analyze optical or other physical properties of a skin lesion and returns a classification of the skin lesion. The device is intended for use by a physician not trained in the clinical diagnosis and management of skin cancer as an adjunctive second-read device following identification of a suspicious skin lesion. It is not for use as a standalone diagnostic and is not for use to confirm a clinical diagnosis.

(b) **Classification**. Class II (special controls). The special controls for this device are:

(1) Data obtained from premarket clinical performance validation testing and post-market surveillance acquired under anticipated conditions of use must demonstrate that the device performs as intended in the intended patient population, unless FDA determines based on the totality of the information provided for premarket review that data from post-market surveillance is not required.

(i) Data must demonstrate superior accuracy of device-aided users' diagnostic characterization of the indicated lesions compared to the accuracy of un-aided users.

(ii) Clinical testing must evaluate patients across a range of skin phototypes, risk factors, and anatomic areas that represents the intended use population.

(iii) Standalone device performance testing must demonstrate the accuracy of the device output relative to ground truth, including the following:

- (A) Testing must demonstrate at least 90% sensitivity of the device output for lesions with high metastatic potential, or an alternative clinical consideration must be provided to justify lower sensitivity. Clinical justification must be provided for the reported specificity.
- (B) Lesions must be selected by representative users and include a justified quantity and range of mimic lesions per diagnosis.
- (C) Justification must be provided for the determination of ground truth.

(D) Testing must include a representative range of individuals with diverse risk factors (including age, body site, and skin phototype, and other clinical factors), and analysis of standalone performance must include subgroup analysis by relevant risk factors.

(2) Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use, including compatibility testing of the device software with specific signal or image acquisition hardware. Testing must include a description of compatible hardware and processes, pre-specified compatibility testing protocols and dataset(s).

(3) Performance testing must demonstrate device precision, including repeatability and reproducibility of device performance, across operators and challenging use conditions.

(4) Performance testing must demonstrate the electrical safety, mechanical safety, thermal safety, and electromagnetic compatibility of any electrical components of the device.

(5) Performance testing must validate reprocessing instructions for reusable components of the device.

(6) The patient-contacting components of the device must be demonstrated to be biocompatible.

Table 1: Product codes associated with 21 CFR 878.1830 for "Software-aided adjunctive diagnostic device for use by physicians on lesions suspicious for skin cancer."

Product Code	Submission Type	Device Type Name	Definition
QZS	510(k)	Software-Aided Adjunctive Diagnostic Device For Use By Physicians On Lesions Suspicious For Skin Cancer	A software-aided adjunctive diagnostic device for use by physicians on lesions suspicious for skin cancer is a prescription device that uses a software algorithm to analyze optical or other physical properties of a skin lesion and returns a classification of the skin lesion. The device is intended for use by a physician not trained in the clinical diagnosis and management of skin cancer as an adjunctive second-read device following identification of a suspicious skin lesion. It is not for use as a standalone diagnostic and is not for use to confirm a clinical diagnosis.

Table 2: Most recent FDA-authorized devices: "Software-Aided Adjunctive Diagnostic Device For Use By Physicians On Lesions Suspicious For Skin Cancer"

Submission	Sponsor	Device	Date Decision
DEN230008	DERMASENSOR	DermaSensor	2024-01-12

B.2 PMA devices

Table 3: Product codes associated with PMA SLAs.

Product Code	Submission Type	Device Type Name	Definition
ONV	PMA	Electrical Impedance Spectrometer	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. 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.
OYD	PMA	Optical Diagnostic Device For Melanoma Detection	Intended in the detection of melanoma and high grade lesions among atypical lesions in order to rule-out melanoma.

Table 4: Most recent FDA-authorized devices: PMA SLAs.

Submission	Sponsor	Device	Date Decision
P150046/S004	SCIBASE	Nevisense	2020-04-30
P150046/S002	SCIBASE	Nevisense	2019-01-14
P150046/S003	SCIBASE	Nevisense	2018-12-11
P150046/S001	SCIBASE	Nevisense	2018-07-13
P150046	SCIBASE	NEVISENSE	2017-06-28
P090012/S011	STRATA SKIN SCIENCES	MELAFIND	2016-08-18
P090012/S010	STRATA SKIN SCIENCES	MELAFIND	2016-03-02
P090012/S006	STRATA SKIN SCIENCES	MELAFIND	2016-01-12
P090012/S004	STRATA SKIN SCIENCES	MELAFIND	2015-10-22
P090012/S008	STRATA SKIN SCIENCES	MELAFIND	2015-01-26
P090012/S005	STRATA SKIN SCIENCES	MELAFIND	2014-12-19
P090012/S007	STRATA SKIN SCIENCES	MELAFIND	2014-11-26
P090012/S003	STRATA SKIN SCIENCES	MELAFIND	2014-10-22
P090012/S009	STRATA SKIN SCIENCES	MELAFIND	2014-07-07
P090012/S002	STRATA SKIN SCIENCES	MELAFIND	2012-10-02

Table 4: Most recent FDA-authorized devices: PMA SLAs. *(continued)*

Submission	Sponsor	Device	Date Decision
P090012/S001	STRATA SKIN SCIENCES	MELAFIND	2012-08-08
P090012	STRATA SKIN SCIENCES	MELAFIND	2011-11-01

C Common acronyms and abbreviations

Table 5: Acronyms and Abbreviations

Term	Description
510(k)	Premarket notification
AI	Artificial intelligence
AIC	Automated Impella Controller
AUROC	Area under the receiver operating characteristics (ROC) curve
CADe	Computer assisted detection
CADx	Computer assisted diagnosis
CDRH	FDA's Center for Devices and Radiological Health
CDS	Clinical decision support
CFR	Code of Federal Regulations
CGM	Continuous glucose monitoring
CGMP	Current Good Manufacturing Practices
DSF	Device software function (a use or function that is a focus of the FDA's oversight)
Dx	Diagnosis
EHR	Electronic Health Record
FDA	U.S. Food and Drug Administration
FD&C Act	Food, Drug, and Cosmetic Act
HCP	Healthcare professional
HHS	U.S. Department of Health and Human Services
IDE	Investigational Device Exemption
IMDRF	International Medical Device Regulators Forum
IRB	Institutional Review Board
MDDS	Medical device data system
MDR	Medical device report
ML	Machine learning
NPA	Negative percent agreement
NPV	Negative predictive value
NSE	Not substantially equivalent
ONC	HHS Office of the National Coordinator for Health Information Technology
OTC	Over-the-counter
PCCP	Predetermined change control plan
PMA	Premarket Approval
PPA	Positive percent agreement
PPV	Positive predictive value
Pre-Cert	Software Precertification (Pre-Cert) Pilot Program
QSR	Quality Systems Regulation (effective 1997-06-01 through 2026-02-01)
SE	Substantially equivalent

SaMD	Software As a Medical Device
TCET	Transitional Coverage of Emerging Technology

References

[1] "87 FR 32172: General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee; Notice of Meeting; Establishment of a Public Docket; Request for Comments," U.S. Food and Drug Administration, Federal Register Notice: Notice of Meeting. Docket Number FDA-2022-N-0589, May 2022. [Online]. Available: https://www.federalregister.gov/d/2022-11420

[2] "87 FR 39025: General and Plastic Surgery Devices; Reclassification of Optical Diagnostic Devices for Melanoma Detection and Electrical Impedance Spectrometers, to be renamed Computer-Aided Devices Which Provide Adjunctive Diagnostic Information About Lesions Suspicious for Melanoma," U.S. Food and Drug Administration, Federal Register Notice: Proposed Rule. Docket Number FDA-2022-N-0794, Jun. 2022. [Online]. Available: https://www.federalregister.gov/d/2022-13954

[3] "De Novo classification process (evaluation of automatic class III designation)," U.S. Food and Drug Administration, Final Guidance Document. Docket Number FDA-2011-D-0689, Oct. 2021. [Online]. Available: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/de-novo-classification-process-evaluation-automatic-class-iii-designation

[4] "Medical devices: Quality management systems: Requirements for regulatory purposes," International Organization for Standardization, International Standard. ISO 13485:2016, Mar. 2016. [Online]. Available: https://www.iso.org/standard/59752.html

[5] "Design control guidance for medical device manufacturers," U.S. Food and Drug Administration, Final Guidance Document. Docket Number FDA-2020-D-0957, Mar. 1997. [Online]. Available: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/design-control-guidance-medical-device-manufacturers

[6] "Software as a medical device (SaMD): Key definitions," International Medical Device Regulator's Forum, Technical Document IMDRF/SaMD WG/N10FINAL:2013, Dec. 18, 2013. [Online]. Available: https://www.imdrf.org/documents/software-medical-device-samd-key-definitions

[7] "The software precertification (Pre-Cert) pilot program: Tailored total product lifecycle approaches and key findings," U.S. Food and Drug Administration, Report. Sep. 2022. [Online]. Available: https://www.fda.gov/medical-devices/digital-health-center-excellence/digital-health-software-precertification-pre-cert-pilot-program

[8] "Good machine learning practice for medical device development: Guiding principles," U.S. Food and Drug Administration, Report. Oct. 2021. [Online]. Available: https://www.fda.gov/medical-devices/software-medical-device-samd/good-machine-learning-practice-medical-device-development-guiding-principles

[9] "Predetermined change control plans for machine learning-enabled medical devices: Guiding principles," U.S. Food and Drug Administration, Health Canada, and the U.K. Medicines and Healthcare products Regulatory Agency, Report. Oct. 2023. [Online]. Available: https://www.fda.gov/medical-devices/software-medical-device-samd/predetermined-change-control-plans-machine-learning-enabled-medical-devices-guiding-principles

[10] "Marketing submission recommendations for a predetermined change control plan for artificial intelligence/machine learning (AI/ML)-enabled device software functions," U.S. Food and Drug Administration, Draft Guidance Document. Docket Number FDA-2022-D-2628, Apr. 2023. [Online]. Available: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/marketing-submission-recommendations-predetermined-change-control-plan-artificial

[11] "Postmarket management of cybersecurity in medical devices," U.S. Food and Drug Administration, Final Guidance Document. Dec. 2016, Docket number FDA-2015-D-5105. [Online]. Available: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postmarket-management-cybersecurity-medical-devices

[12] "Cybersecurity in medical devices: Quality system considerations and content of premarket submissions," U.S. Food and Drug Administration, Final Guidance Document. Sep. 2023, Docket number FDA-2021-D-1158. [Online]. Available: https://www.regulations.gov/document/FDA-2021-D-1158-1880

[13] "Select updates for the premarket cybersecurity guidance: Section 524B of the FD&C Act," U.S. Food and Drug Administration, Draft Guidance Document. Mar. 2024, Docket number FDA-2021-D-1158. [Online]. Available: https://www.regulations.gov/document/FDA-2021-D-1158-1882

[14] "Content of premarket submissions for device software functions," U.S. Food and Drug Administration, Final Guidance Document. Jun. 2023, Docket number FDA-2021-D-0775. [Online]. Available: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/content-premarket-submissions-device-software-functions

[15] "Significant risk and nonsignificant risk medical device studies," U.S. Food and Drug Administration, Final Guidance Document. Docket Number FDA-2006-D-0031, Jan. 2006. [Online]. Available: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/significant-risk-and-nonsignificant-risk-medical-device-studies

[16] "Breakthrough devices program," U.S. Food and Drug Administration, Final Guidance Document. Docket Number FDA-2017-D-5966, Sep. 2023. [Online]. Available: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/breakthrough-devices-program

[17] "Requests for feedback and meetings for medical device submissions: The Q-submission program," U.S. Food and Drug Administration, Final Guidance Document. Docket Number FDA-2018-D-1774, May 2025. [Online]. Available: https://www.regulations.gov/document/FDA-2018-D-1774-0063

[18] "The 510(k) program: Evaluating substantial equivalence in premarket notifications [510(k)]," U.S. Food and Drug Administration, Final Guidance Document. Docket Number FDA-2011-D-0652, Jul. 2014. [Online]. Available: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/510k-program-evaluating-substantial-equivalence-premarket-notifications-510k

[19] "FDA and industry actions on premarket notification (510(k)) submissions: Effect on FDA review clock and goals," U.S. Food and Drug Administration, Final Guidance Document. Docket Number FDA-2003-D-0033, Oct. 2022. [Online]. Available: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-and-industry-actions-premarket-notification-510k-submissions-effect-fda-review-clock-and-goals

[20] "Electronic submission template for medical device 510(k) submissions," U.S. Food and Drug Administration, Final Guidance Document. Docket Number FDA-2021-D-0872, Oct. 2023. [Online]. Available: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/electronic-submission-template-medical-device-510k-submissions

[21] "FDA and industry actions on De Novo classification requests: Effect on FDA review clock and goals," U.S. Food and Drug Administration, Final Guidance Document. Docket Number FDA-2017-D-5712, Oct. 2022. [Online]. Available: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-and-industry-actions-de-novo-classification-requests-effect-fda-review-clock-and-goals

[22] "Modifications to devices subject to premarket approval (PMA) – the PMA supplement decision-making process," U.S. Food and Drug Administration, Final Guidance Document. Docket Number FDA-2007-D-0025, Oct. 2008. [Online]. Available: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/modifications-devices-subject-premarket-approval-pma-pma-supplement-decision-making-process

[23] "FDA and industry actions on premarket approval applications (PMAs): Effect on FDA review clock and goals," U.S. Food and Drug Administration, Final Guidance Document. Docket Number FDA-2003-D-0378, Oct. 2022. [Online]. Available: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-and-industry-actions-premarket-approval-applications-pmas-effect-fda-review-clock-and-goals