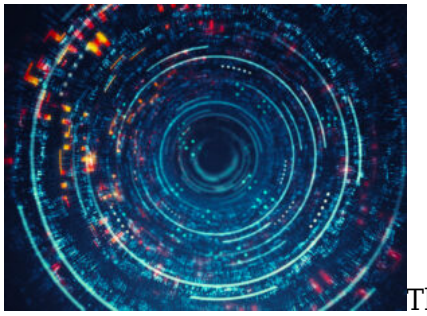
FDA Issues Artificial Intelligence/Machine Learning (AI/ML)-Enabled Device Software Functions Draft Guidance



The U.S. Food and Drug Administration recently issued its **draft guidance** entitled "Marketing Submission Recommendations for a Predetermined Change Control Plan for Artificial Intelligence/Machine Learning (AI/ML)-Enabled Device Software Functions." The draft guidance follows the passage of the Food and Drug Omnibus Reform Act of 2022 (FDORA), which explicitly authorized the Agency to approve or clear Predetermined Change Control Plans (PCCPs).

We summarize some of the key takeaways from FDA's draft guidance. Read the client alert **here**.

FDA Issues Guidance Document on Animal Studies for the Evaluation of Medical Devices

The U.S. Food and Drug Administration (FDA) recently issued **General Considerations for Animal Studies Intended to Evaluate Medical Devices – Guidance for Industry and Food and Drug Administration Staff (fda.gov)**. Following a 2015 draft guidance and replacing a 2010 guidance focused on animal studies for cardiovascular devices, this guidance document identifies general considerations for animal studies intended to provide evidence of safety, including performance and handling, in device premarket submissions "when a suitable alternative to an animal study is not available." Among other topics, the guidance provides

recommendations related to personnel credentials, selecting an appropriate animal model, testing facility selection, and how to prepare an animal study report for premarket submissions to FDA. The Agency encourages sponsors with specific questions on an animal study, including the animal model selected, or compliance with FDA's Good Laboratory Practice (GLP) regulations, or who seek to use a non-animal testing method, to request feedback from FDA through the Q-Submission process.

Avoiding Misbranding: Words Matter When Describing the Regulatory Status of 510(k) Cleared Devices and Registered Device Establishments

 When it comes to discussing medical devices regulated by the U.S. Food and Drug Administration (FDA), words such as "approved" and "cleared" cannot be used interchangeably as these terms carry a particular meaning. Similarly, creating an impression of approval of a device establishment or its devices because the establishment is registered with FDA also is prohibited. Long-standing regulatory provisions, **21 C.F.R. § 807.97** and **21 C.F.R. § 807.39**, set forth, respectively, the FDA's position that approval and clearance are not interchangeable and that device establishment registration does not denote approval of the establishment or its devices. Importantly, these provisions also highlight the consequences to industry for misusing terms when discussing the regulatory status of a device or a device establishment.

When seeking to market a new device for which a premarket notification must be submitted to the FDA demonstrating that the device to be marketed is substantially equivalent to a legally marketed device, the submitter must obtain an order of substantial equivalence from the FDA, which is commonly referred to as a 510(k) *clearance*. Conversely, to market a new device for which a premarket approval application must be submitted to the FDA, the applicant must obtain FDA's *approval* of the application. While FDA review and FDA action occur for both types of medical devices, the outcomes of clearance and approval are distinctly different and carry legal consequences. Specifically, 21 C.F.R. § 807.97 states that "[a]ny representation that creates an impression of official approval of a device because of complying with the premarket notification regulations is misleading and constitutes misbranding." Additionally, 21 C.F.R. § 807.39 states that "[a]ny representation that creates an impression of official approval because of registration or possession of a registration number is misleading and constitutes misbranding."

We researched Warning Letters in **FDA's Warning Letter Database** and found that FDA issued

four Warning Letters citing violations of § 807.97 since 2017 and thirteen Warning Letters citing violations of § 807.39 since 2017.

Many of the representations that FDA found to be misleading under § 807.97 were straightforward violations, such as language on product websites stating that cleared devices are "FDA approved," or listings of device clearances under the heading "FDA Approvals." In one instance, FDA found the website to be misleading under both § 807.39 and § 807.97 because the company claimed the device had been cleared by the FDA, when in fact it was marketing a 510(k) exempt device for an indication that would require a de novo authorization which the company had not obtained, and the website claimed the company maintained an active listing, which was hyperlinked to the company's FDA Establishment Registration and Device Listing for only the 510(k) exempt device.

In response to the COVID-19 public health emergency, FDA issued twelve Warning Letters related to representations regarding masks and antibody tests that were found to be misleading under § 807.39. In virtually all of these instances, company websites displayed unofficial "certificates of FDA registration" issued by third parties which claimed to certify that the manufacturer had completed FDA Establishment Registration and Device Listing. These certificates often incorporated unauthorized reproductions of FDA's logo and motifs of the U.S. flag, giving the impression of official government documents. FDA consistently found the display of these certificates to be misleading, even when they included ostensible "disclaimer" language stating that the certificates did not denote FDA endorsement or approval. FDA repeatedly found that these disclaimers did not adequately limit or otherwise mitigate the misleading impression of the certificates because they were phrased, designed, and placed in a manner where they could be easily overlooked.

These Warning Letters present a cautionary tale to all sponsors intending to market new medical devices. While sponsors may be tempted to claim their devices are approved by the FDA following the agency's review of a premarket notification or upon completion of FDA Establishment Registration and Device Listing, § 807.97 and § 807.39 make clear that such claims will constitute misbranding. Sponsors can avoid § 807.97- and § 807.39-related Warning Letters and associated liability by carefully reviewing all of the language on their marketing materials and websites to ensure that none of their representations create the impression of official approval based on reference to a premarket notification submission or establishment registration.

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Potential AI/ML Learnings to Come from FDA Public Advisory Committee Meeting on Skin Lesion Analyzer Technology in Late July

 On July 28, 2022, the U.S. Food and Drug Administration (FDA) will hold a public advisory committee meeting to discuss skin lesion analyzer (SLA) technology and its application to detecting skin cancers in various patient care settings. This meeting of the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee will focus on algorithm-based SLA devices for adjunctive detection of skin lesions, including skin cancers, and stands to provide industry another layer of thinking on FDA's perspective on artificial intelligence and machine learning (AI/ML) device technologies.

In announcing this meeting, FDA explained that in recent years it has observed an increased interest in SLA devices employing AI/ML. The agency is seeking expert input from the panel on approaches to evaluate the performance of SLA devices, which have a range of technologies and indications.

The committee will discuss and provide recommendations to FDA on: (1) the diagnosing standard, or ground truth, that should be used as a comparison for the performance of diagnostic devices, e.g., histology, consensus opinion of a panel of dermatologists, opinion of a single dermatologist, or other means; (2) acceptable sensitivity and specificity thresholds based on the target diagnosis (melanoma, basal cell carcinoma, squamous cell carcinoma) or intended user (dermatologist, primary care physician, lay user); (3) patient characteristics, including lower or higher incidence populations, that should be tested before marketing; and (4) the balance of increased access with risk mitigation measures that are appropriate when the devices are used by lay people, by populations with very high or very low incidence of melanoma, by populations with low incidence, but high mortality associated with melanoma, or by the target diagnosis/lesion type.

Additionally, on July 29, 2022, the committee will discuss the possible reclassification of two class III, PMA approved computer-aided melanoma detection devices, MelaFind (P090012) and Nevisense (P150046), both of which are intended for use on cutaneous lesions suspicious for melanoma when a dermatologist chooses to obtain additional information when considering biopsy. According to the FDA announcement, "The committee will discuss if there is sufficient information to reclassify computer-aided devices for adjunctive diagnostic information of lesions suspicious for melanoma from class III to class II, and what special controls may be appropriate to provide reasonable assurance of safety and effectiveness" if they are reclassified.

This meeting, and any actions the FDA takes as a result, could offer industry further insight into the FDA's approach to regulating AI/ML diagnostic and screening products more broadly.

The meeting will be held virtually on July 28, 2022, from 9 am to 5:45 pm ET and July 29, 2022, 9 am to 4 pm ET. Comments received on or before July 11, 2022 will be provided to the committee and the public docket will remain open for comment for FDA's consideration until August 29, 2022.

For more information see the **Meeting Notice on the Federal Register**.

Highlights for SaMD Developers: FDA's January 2021 Artificial Intelligence/Machine Learning Action Plan

 On January 12, 2021, the U.S. Food and Drug Administration (FDA) published its **Action Plan** for further development of the Agency's framework for regulatory oversight of artificial intelligence (AI) and machine learning (ML) based Software as a Medical Device (SaMD). The Action Plan identifies several opportunities for SaMD developers to engage the FDA as its regulatory framework for AI/ML-based SaMD oversight evolves:

- **Predetermined Change Control Plans:** FDA remains committed to refining a regulatory framework that would allow for some post-market SaMD modifications based largely on the establishment and utilization of SaMD Pre-Specifications (SPS) and an Algorithm Change Protocol (ACP) set forth in a "Predetermined Change Control Plan." SaMD developers can expect, and be ready to submit comments on, a draft guidance in 2021 addressing a Predetermined Change Control Plan.
- **Real-World Performance:** Real-world data collection and monitoring is another key concept in FDA's proposed regulatory framework for oversight of modifications to AI/ML-based SaMD. FDA plans to advance real-world performance monitoring pilots with stakeholders on a voluntary basis, and use the learnings from these activities to develop a framework for gathering and validating relevant real-world performance parameters and metrics.
- **Algorithm Transparency:** To identify types of information that FDA may recommend SaMD developers include in the labeling of their AI/ML-based devices, FDA intends to hold a public workshop to elicit input from the broader community on how device labeling supports transparency to users.

FDA also will continue to participate in global working groups focused on harmonizing principles of Good Machine Learning Practice (GMLP) as well as expand upon the Agency's efforts to develop methods for evaluating and addressing algorithmic bias.

The Agency recognizes that continued stakeholder engagement will be crucial for the formation of a sensible regulatory framework for oversight of AI/ML-based SaMD. SaMD developers seeking to inform the development of FDA's regulatory framework are strongly encouraged to participate in the specific opportunities outlined in the Action Plan.

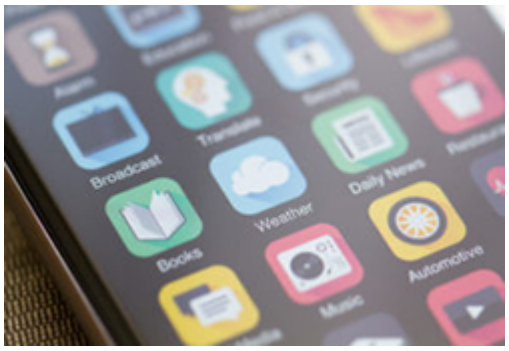
The Continuing Saga of Lab Developed Tests, Including for COVID-19 Testing

In August, the U.S. Department of Health & Human Services (HHS) **announced** that the FDA will not require premarket review of laboratory developed tests (LDTs), whether COVID-19 related or not, absent notice-and-comment rulemaking. Labs may voluntarily seek a premarket approval, 510(k) clearance, or an emergency use authorization (EUA) for their LDTs. Importantly, labs that do not obtain such FDA approval, clearance, or authorization would not be eligible for **PREP Act** coverage.

This announcement may have come as a surprise to FDA, which historically has asserted its medical device regulatory authority over LDTs while often subjecting them to enforcement discretion. Despite this HHS announcement, FDA's May 11, 2020 **Policy for Coronavirus Disease-2019 Tests During the Public Health Emergency** remains in effect and has not been revised since the announcement. Importantly, this guidance offers two pathways for COVID-19 related LDTs – an EUA submission to FDA and the development of an LDT under the authorities of the State in which the laboratory resides, where the State takes responsibility for COVID-19 testing by labs in its State.

For FDA's latest statements on COVID-19 testing, see the **opinion piece** authored by CDRH Director Dr. Jeffrey Shuren and Dr. Timothy Stenzel, Director of the Office of Health Technology 7, In Vitro Diagnostics and Radiological Health, in the Hill.

FDA's COVID-19 Enforcement Policy for Digital Health Devices for Treating Psychiatric Disorders



Developers of certain digital health devices for treating psychiatric disorders may be able to take advantage of an FDA **enforcement policy**, which remains in effect for the duration of the COVID-19 public health emergency. The policy applies to certain prescription computerized behavioral therapy (CBT) devices for psychiatric disorders, digital health therapeutic devices for psychiatric disorders that operate using a different fundamental technology than CBT, other variations of CBT devices, such as non-prescription devices, and low-risk general wellness and digital health products for mental health or psychiatric conditions.

Relevant psychiatric conditions include Obsessive Compulsive Disorder, Generalized Anxiety Disorder, Insomnia Disorder, Major Depressive Disorder, Substance Use Disorder, Post-traumatic Stress Disorder, Autism Spectrum Disorder, and Attention Deficit Hyperactivity Disorder. The enforcement policy's goal is "to help expand the availability" of these devices to aid those with these conditions "while reducing user and healthcare provider contact and potential exposure to COVID-19."

Under this policy, these devices may be distributed and used without complying with the following regulatory requirements, where such devices do not create an undue risk in light of the public health emergency: 510(k) submission, correction and removal reports, registration and listing requirements, and Unique Device Identification requirements. For those software products with low-risk general wellness indications or functionality, FDA does not intend to enforce regulatory requirements consistent with the agency's existing policies, which were in effect prior to the pandemic. Finally, FDA's enforcement policy sets forth certain recommendations regarding the performance and labeling elements for these devices, such as user instructions that direct the patient to contact a physician before using the device. This enforcement policy highlights FDA's regulatory flexibility for software and app developers in this therapeutic area during the COVID-19 pandemic.

Q&A on FDA's Requirements Related to Financial Disclosure by Clinical Investigators

What financial arrangements between clinical trial sponsors and clinical investigators must be disclosed in a drug, biologic or device marketing application?

In a marketing application, FDA requires that four types of financial arrangements be disclosed: (1) any financial arrangement between the sponsor and the investigator whereby the value of the compensation to the investigator for conducting the study could be influenced by the outcome of the study; (2) any significant payments of other sorts from the sponsor, such as a grant to fund ongoing

research, compensation in the form of equipment, a retainer for ongoing consultation, or honoraria, which are greater than $25,000 in cumulative value and given to the investigator or the investigator's institution to support the investigator's activities, exclusive of the costs of conducting the study, for the duration of the study and for one year following the study's completion; (3) any proprietary interest in the tested product held by the investigator; and (4) any significant equity interest in the sponsor held by the investigator, which is any amount for a non-publicly traded company or an equity interest in a public company valued over $50,000 for the duration of the study and for one year following the study's completion.

How is a clinical investigator defined in the context of FDA financial disclosure regulations?

In FDA's financial disclosure regulations, the agency defines a clinical investigator as a listed or identified investigator or sub-investigator who is directly involved in the treatment or evaluation of research subjects. The term also includes the spouse and each dependent child of the investigator.

What does FDA look for with regard to financial interest?

FDA looks at several factors with regard to financial interest, including the size and nature of the disclosed financial interest, the steps taken to minimize the potential for bias, and the study design. For example, FDA will evaluate whether the study has been designed with multiple investigators (most without a disclosable interest), blinding, objective endpoints, or measurement of endpoints by someone other than the investigator. FDA may initiate audits of the data from the investigator at issue, request that the applicant submit further analyses of the data or conduct additional independent studies to confirm the results. The agency could also refuse to treat the study as providing data that can be the basis for an agency action. We recommend you contact your Goodwin life sciences or FDA lawyer for further explanation of the agency's financial disclosure regulations.