



FDA Regulation of AI: Compliance and other Considerations

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Agenda

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- 1 Background and FDA Definition/Classification of Medical Devices
 - 2 FDA Policies, Guidances and Special Controls Specific to Digital Health and AI
 - 3 Recent Developments
 - 4 Regulatory Requirements, Examples and Related Compliance
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FDA Focus on Digital Health: Digital Health Innovation Plan

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- Digital Health Statutory Changes: 21st Century Cures Act (Dec 2016)
- Digital Health Innovation Action Plan (June 2017)
- Pre-Certification (Pre-Cert) Program Announced (Aug 2017)
- 21st Century Cures implementation: 2 draft guidances (Dec 2017)
- Commissioner announces more DH/AI initiatives (April 2018)
- Multiple Function Products Draft Guidance (April 2018)
- Pre-Cert Program Model (April 2018); Version 2.0 (June 2018)
- Medical Device Safety Action Plan (April 2018)
- Safer Technologies Program for Medical Devices Draft Guidance (September 2019)

FDA Definition and Classification of Medical Devices

U.S. FDA Medical Device Definition

- A product is regulated if it meets the definition of a medical device in FDA's statute
 - Definition (§ 201(h) of the Federal Food, Drug and Cosmetic Act (FFDCA)):
 - Instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or component that is:
 - Recognized in USP or other compendia,
 - Intended for use in diagnosis of disease or other conditions,
 - Intended for use in the cure, mitigation, treatment, or prevention of disease, or
 - Intended to affect structure or function of the body, and
 - Which does not achieve its primary intended purposes through chemical action on or within the body and which is not dependent on being metabolized.
- **Intended use** is central in determining whether a product falls within the definition of a medical device
 - Based on intent of manufacturer
 - Determined from labeling claims, promotional material, oral/written statements by company representatives

When Does A Product Become A Medical Device?

- A single product could be either regulated or unregulated depending on intended use:
- Examples:
 - Heart Rate Monitor –
 - Regulated – monitor patient health
 - Unregulated – use in fitness
 - Standalone Software
 - Regulated – AI algorithm to triage images for urgent review
 - Unregulated – AI algorithm for clinical research use only



Possible Regulatory Pathways for Digital Health/Software/AI Products

- FDA regulates digital health products, including standalone software, pursuant to the same risk-based framework as other medical devices.
 - Companies can evaluate FDA precedent for regulation of similar products to help determine the most appropriate regulatory pathway for a new digital health/software/AI product
 - **FDA's traditional paradigm of medical device regulation was not designed for adaptive artificial intelligence and machine learning technologies.**
 - Under the FDA's current approach to software modifications, FDA anticipates that many o artificial intelligence and machine learning-driven software changes to a device may need a premarket review.

Possible Regulatory Pathways for Digital Health/Software/AI Products

- Several possible regulatory pathways:
 - Product is not a medical device (*i.e.*, no FDA regulation)
 - Digital health/software that does not meet the updated FDC Act definition of a device is considered a consumer product
 - Product is subject to enforcement discretion (*i.e.*, no active FDA oversight)
 - Product is actively regulated as a medical device (class I, II or III)
 - In general, subject to same pre- and post-market regulations as any other medical device.
 - Certain types of software products may have particular additional requirements.
 - Product is regulated as a combination product (combination of drug, device, and/or biologic)

Factors FDA Uses in Classifying Digital Health/AI Products

- Key factors considered by the agency in determining whether a digital health/software/AI products is regulated include:
 - The degree of impact on the patient
 - The greater the impact, the more likely it is to be regulated as a medical device.
 - *E.g.*, products that control the function of another medical device, transform a mobile platform into a regulated medical device, or provides a diagnosis, are likely to be actively regulated.
 - The level of risk presented to the user/patient (*e.g.*, what type of medical purpose it is used for; how any results generated by the product will be used; etc.)
 - Whether performs patient-specific analysis and/or provides patient-specific diagnosis or treatment recommendations
 - **Ethical Consideration: Clinical Utility and Related Performance – also questioned by FDA**

Factors FDA Uses in Classifying Digital Health Products

- Key factors considered by the agency in determining whether a digital health/software/AI product is regulated include:
 - Whether the product is used in active patient monitoring
 - Devices intended to trigger immediate clinical action (*e.g.*, certain real-time monitoring products that generate alerts for important physiological changes) require premarket clearance/approval, unless limited to MDDS functionalities
 - Whether the product generates independent analysis or merely performs a reviewable task on behalf of a clinician
 - If the software performs an analysis that the user could not independently derive (*e.g.*, through application of a proprietary algorithm), premarket clearance/approval is likely required
 - AI Software can be a black box
 - By contrast, software that assesses patient data/results per established clinical guidelines (*e.g.*, whether certain symptoms meet the definition of diabetes) is no longer considered a device

FDA Device Classifications

- If a product is a medical device, possible options:
 - Under enforcement discretion
 - Could be with respect to all FDA requirements or only certain requirements (e.g., premarket clearance/approval)
 - Classification in one of 3 risk-based classes, which determine regulatory burden

Class I	Class II	Class III
Low Risk	Moderate Risk	High Risk
General Controls	General & Special Controls	General Controls & demonstrate safety and effectiveness
Generally exempt from clearance/ approval	510(k) Clearance (“substantially equivalent” to a “predicate” device)	PMA Approval (must prove safety and effectiveness)

- Novel products default into class III and, if low or moderate risk, can be reclassified into class I or II via de novo pathway

FDA Policies, Guidances and Special Controls Specific to Digital Health

FDA Regulatory Framework: Digital Health/Software/AI

- The current scope of FDA regulation of digital health and software products is largely defined by FDA guidance documents and recent legislative developments, including:
 - *Mobile Medical Applications* (2015 guidance followed by 2019 guidance)
 - *General Wellness: Policy for Low Risk Devices* (2016 guidance)
 - 21st Century Cures Act (enacted December 2016) narrowed FDA’s jurisdiction over 5 categories of health and medical software functions
 - *Multiple Function Device Products: Policy and Considerations* (Draft Guidance April 2018)
 - *Changes to Existing Medical Software Policies Resulting from Section 3060 of the 21st Century Cures (2019)*
 - *Clinical and Patient Decision Support Software* (2019)
 - *Medical Device Data Systems, Medical Image Storage Devices, and Medical Image Communications Devices* (2019)
 - *Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) - Discussion Paper and Request for Feedback*
 - Special Controls from De Novo AI Devices (i.e., *Viz.AI ContaCT DEN170073* (CADt); *OsteoDetect DEN180005* (CADE)) – Differs slightly from other software devices in manner of regulation

21st Century Cures

- Modified statutory definition of “medical device” to exclude:

Administrative Software	Health and Wellness	Electronic Health Records	MDDS + Functionality	Clinical Decision Support
Examples <ul style="list-style-type: none">•Billing•Scheduling	Must be unrelated to medical purposes	If created by a healthcare provider, and fits within the Health IT certification under section 3001(c)(5) of the Public 20 Health Service Act No analysis functions	Includes lab data and “findings” by a healthcare professional and associated “background information”	Must be transparent and not intended to be the sole basis for a determination. Not analyzing laboratory, imaging or sensor data.

- AI software functionality likely outside the above exemptions and regulated as a medical device
- Examples:
 - Artificial intelligence system that identifies hospitalized patients with type 1 diabetes who may be at risk for cardiovascular events
 - Algorithm that categorizes likely cases of seasonal influenza, using electronic medical records and geographic data, by screening them out from patients with common flu or cold symptoms

Clinical Decision Support (CDS) Tools

- 21st Century Cures Act signed into law in December 2016
 - Included changes to the definition of a medical device to exclude from regulation certain types of medical software, including some types of CDS
- FDA Guidance, Clinical and Patient Decision Support Software (CDS Guidance), issued by FDA in September 2019
 - Interprets Cures Act changes and explains proposed FDA policy for CDS

Section 3060(a) of the Cures Act

- CDS tools meeting all of the following four criteria are no longer considered devices subject to FDA regulation:
 1. Not intended to acquire, process, or analyze a medical image or a signal from an in vitro diagnostic device or a pattern or signal from a signal acquisition system;
 - Most AI software would not meet this prong
 2. Intended to display, analyze, or print medical information about a patient or other medical information (such as peer-reviewed clinical studies and clinical practice guidelines);
 3. Intended for the purpose of supporting or providing recommendations to a health care professional about prevention, diagnosis, or treatment of a disease or condition; and
 4. Intended to enable such health care professional to independently review the basis for such recommendations that such software presents so that it is not the intent that such health care professional rely primarily on any of such recommendations to make a clinical diagnosis or treatment decision regarding an individual patient.
 - Most AI software would not meet prong 4 and thus would not be an exempted CDS tool
 - Block box software

- Examples of CDS that remain devices and on which FDA intends to focus its regulatory oversight include, among others, software that:
 - Uses a patient’s images (e.g., CT or MRI) to create an individual plan for radiation therapy treatment, where the health care professional is meant to rely primarily on the plan when determining how to treat the patient;
 - Manipulates or analyzes radiological images and other data to create 3D models intended to be used in planning surgical treatments;
 - Analyzes sound waves to diagnose bronchitis or sinus infection;
 - Employs an undisclosed algorithm to analyze patient information to determine which drug class is likely to be most effective in lowering a patient’s blood pressure
 - AI software used to screen embryo development and likely success upon implantation

Function-by-Function Approach to Digital Health

- FDCA regulates articles (e.g., drug, device) based on the intended use(s) of the article
 - 21st Century Cures directs FDA to regulate software **by function**
 - An article may have more than one “function,” which could be the same as the intended use or a subset of the intended use
 - AI function can be to triage for Large Vessel Occlusion, Intracranial Hemorrhage, Pneumothorax, etc. - each is a different functionality

Multiple Function Products

- April 27th FDA released a new draft guidance:
 - *Multiple Function Device Products: Policy and Considerations*
- Implements multiple function provision of 21st Century Cures
- Also expands to include both hardware and software products
 - Aligns with FDA's existing informal policy
- FDA will focus review (and postmarket obligations) on regulated functions in an integrated product
- Non-device functions (and 510(k)-exempt functions) will only be considered to the extent that they may impact safety/efficacy of regulated functions

Multi-Function Premarket Submissions

- **Indications for Use:** Should cover only the regulated function
- **Device Information:** Include a description of any non-device functions that impact the device function
 - Design documents should include “adequate detail to understand how or if the other functions interact with or impact the device function-under-review”
 - Requirements and specifications should include “adequate detail to describe any expected relationship, utility, reliance, or interoperability with any other function”
- **Risk Analysis:** Include an assessment of the impact of the non-device functions on the regulated function and any risk mitigations

Recent Developments

Development of Pre-Cert Program

- Potentially the most dramatic shift in the FDA's paradigm for digital health products
 - Overlaps with AI White Paper
- Unveiled as part of FDA's Digital Health Innovation Action Plan
- Purpose: to reduce time and cost of market entry for digital health software companies with track record of developing and testing quality products
- Shifting focus to certifying SaMD developers instead of traditional focus on product clearance or approval
- Ultimate implementation: allow pre-certified companies to skip premarket review or undergo streamlined review for new software
- Not yet functioning as intended and parallel submissions needed
 - Mid-year report published with status update:
<https://www.fda.gov/media/129047/download>

Precertification: Excellence Appraisal

- Company submits application for Pre-Certification, which must show how its management system demonstrates the following principles:

Excellence Principle	Definition
Product Quality	Demonstration of excellence in the development, testing, and maintenance necessary to deliver SaMD products at the highest level of quality.
Patient Safety	Demonstration of excellence in providing a safe patient experience and emphasizing patient safety as a critical factor in all decision-making processes.
Clinical Responsibility	Demonstration of excellence in responsibly conducting clinical evaluation and ensuring that patient-centric issues, including labeling and human factors, are appropriately addressed.
Cybersecurity Responsibility	Demonstration of excellence in protecting cybersecurity and proactively addressing cybersecurity issues through active engagement with stakeholders and peers.
Proactive Culture	Demonstration of excellence in a proactive approach to surveillance, assessment of user needs, and continuous learning.

- Company is certified to Level 1 or Level 2

Precertification: Premarket Review Process

Level 1

Company objectively demonstrated excellence in product development in all five Excellence Principles, but has a *limited* track record in developing, delivering and maintaining products in the healthcare space.

Low Risk Software Products: No FDA Review

All Other Software Products: Streamlined FDA Review

Level 2

Company objectively demonstrated excellence in product development in all five Excellence Principles and *has* a track record in developing, delivering and maintaining products in the healthcare space.

Low and Moderate Risk Software Products: No FDA Review

All Other Software Products: Streamlined FDA Review

Precertification: Real-world Performance Monitoring

- Company must have access to information about how its software product is performing with patients to support the regulatory status of the product and new and evolving product functions
- Data will be used to:
 - Monitor safety, effectiveness, and performance of marketed software medical devices
 - Support modifications of clinical and performance claims for safety and effectiveness
 - Providing input on initial company precertification determination and changes to precertification status
 - Provide FDA feedback on how to further refine the Software Precertification Program

Medical Device Safety Action Plan - Cybersecurity

- Announced April 2018, highlighting FDA’s increasing focus on cybersecurity
 - FDA increasingly seeking to review cybersecurity software information and data in premarket submissions for “connected” devices
- FDA requested additional authority and budget allocation for FY 2019 to increase cybersecurity and digital health oversight
 - Subsequently authorized by Congress.
- FDA intends to update its premarket guidance on medical device cyber security to better protect against moderate risks (i.e., those that could disrupt clinical operations and/or delay patient care) and major risks (i.e., those that exploit a vulnerability to enable a remote, multi-patient, catastrophic attack)
- In the postmarket sphere, FDA will consider requiring firms to adopt policies and procedures for coordinated disclosure of cybersecurity vulnerabilities as they are identified
 - Intended to supplement FDA’s existing guidance documents, *Postmarket Management of Cybersecurity in Medical Devices* (Dec. 2016) and *Cybersecurity for Networked Medical Devices Containing Of-the-Shelf (OTS) Software* (May 2005).

Regulatory Requirements for Medical Devices, Examples and Related Compliance

Premarket Clearance or Approval

PMA	De Novo	510(k)
Safety and effectiveness	General and special controls provide reasonable assurance of safety and effectiveness	Substantial equivalence
Must be “approved”	Request “granted”	Must be “cleared”
Valid scientific evidence	Requirements for Class I or II must be met	Comparison to existing (predicate) device
Almost always accompanied by clinical data	Most de novo requests contain clinical data	10-15% contain clinical data
Like a product license or regulatory patent	No exclusivity	No exclusivity
180 days	120 days	90 days
Longer total review (1-2 years)	Medium (9-12 months)	Shorter (6-9 months)

Applicable Premarket and Postmarket Requirements

- Premarket clearance or approval (unless product is exempt by regulation or under E.D.)
- General Controls
 - Prohibitions against adulteration & misbranding
 - Facility registration and device listing
 - Good Manufacturing Practices / Quality System Regulation
 - Record-keeping and reporting requirements
 - Repair, replacement, refund
 - Labeling
- Special Controls (commonly seen with AI software devices as a result of de novo clearances)
 - Performance standards
 - Post-market surveillance
 - Patient registries
 - Guidance documents
 - Recommendations
 - Other FDA actions

Post-market Compliance Obligations

- **Quality System Regulation (QSR)**

- Quality management system (set of procedures) for design, manufacture, packaging, labeling, storage, installation, and servicing
- Covers topics such as:
 - Management responsibility
 - Design controls
 - Acceptance activities
 - Processes to handle nonconforming products
 - Purchasing controls
 - Complaint handling

- **Establishment Registration and Device Listing**

- Must register facility (address) and list all devices made/handled (including specification development) in that facility
- Adds the company to FDA's inspection list

Post-market Compliance Obligations (cont.)

- **Medical Device Reporting**
 - Must report certain adverse events and malfunctions to FDA
 - Included in public database
- **Corrections and removals (Recalls, Field Corrections, etc.)**
 - Must be documented and some must be reported to FDA
 - FDA has authority to require recalls in some cases
- **Labeling and promotion** (*see subsequent slides*)
- **Product modifications**
 - Must be assessed to determine whether new clearance/approval is needed

Labeling, Advertising, and Promotion

- For medical devices, FDA has jurisdiction over labeling; FTC has jurisdiction over advertising (except “restricted” devices).
- Labeling includes: (1) written, printed or graphic information that appears on the device or its immediate container (*i.e.*, label); and (2) descriptive and informational materials that accompany the device, such as posters, tags, pamphlets, circulars, booklets, brochures, etc.
 - “Accompany” does not require a physical connection; the test is whether the material supplements or explains the article or drug. *Kordel v. U.S.*, 333 U.S. 345 (1948).
 - Any material used to facilitate the sale of a device is labeling.
 - Promotional materials generally are considered “labeling”, not advertising.
- Advertising is typically media-related, *e.g.*, newspaper, academic journal, radio, TV.
 - FDA has sought to gain jurisdiction over advertising by calling it labeling

Example AI Devices

Example AI Devices

- Viz.AI ContaCT; DEN170073 - for use in triaging Large Vessel Occlusion for urgent review (Product Code: QAS)
 - Zebra Medical HealthPNX; K190362 – triage findings suggestive of Pneumothorax (Product Code: QFM)
- OsteoDetect; DEN180005 - identify and highlight distal radius fractures during the review of posterior-anterior (PA) and lateral (LAT) radiographs of adult wrists
- Auxogyn Eeva System; DEN120015 - designed to obtain and analyze light microscopy images of developing embryos; provides information to aid in selection of embryo(s) for transfer when there are multiple embryos deemed suitable for transfer or freezing

Each new de novo provides Special Controls for new device regulation

Data Considerations

- Training and validation sets to be kept separate and from different clinical sites or different time points
- Need patient demographics, such as age, sex, ethnicity, etc.
- Cases to be collected consecutively versus randomly selected
- Need guardrails for reusing validation test set as AI algorithm can start to learn from reuse of testing set
- Special controls dictate performance required based on proposed indications for use
 - See product code QAS vs. QFM for CADt devices

Other Considerations

- Periodically revisit internal assessments for digital health products and update as needed
 - Changing regulatory status
- Regulatory status will drive how the products can be presented and promoted, and will also drive the applicability of regulatory controls
- Closely assess any modifications to the digital health products or connected devices that are actively regulated
 - Software and hardware changes that add functionalities could trigger active or additional regulation
- Privacy/HIPAA considerations need to be assessed – even though outside FDA regulation
- Cybersecurity considerations are key and more frequently seen in FDA questions
- Common Pitfall: 510(k) clearances/de novos cannot be licensed so that there would be 2 device manufacturers
 - See the following related Warning Letter: <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/craftmatic-industries-inc-02172015>

Questions and Discussion

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