AI and Digital Pathology: Regulatory Perspective

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Disclosures

- No financial relationships to disclose

- The views expressed during this presentation are those of the presenter and do not necessarily reflect the policy or position of the US FDA or the US government

Division of Molecular Genetics and Pathology
DMGP/OIR (OHT-7)/CDRH/FDA

Oversees the regulation of digital pathology medical devices

- Provides regulatory feedback to device manufacturers during the development, validation and marketing of digital pathology devices

- Reviews marketing applications and authorizes marketing of these devices

- FDA regulatory point of contact

Overview

- Current FDA Review Framework
- Digital Health: Current FDA Efforts
- Artificial Intelligence (AI) based digital pathology devices: Regulatory perspective

Current FDA Review Framework

- An appropriate premarket pathway:
  - Premarket clearance (510(k))
  - De Novo classification
  - Premarket approval

- Certain modifications to medical devices, including software as a medical device (SaMD) requires a marketing application: refer to FDA guidance "*Deciding When to Submit a 510(k) for a Software Change to an Existing Device*"

https://www.fda.gov/media/99785/download

Definitions

- **Artificial Intelligence (AI):** *"A device or product that can imitate intelligent behavior or mimics human learning and reasoning."*

  AI includes machine learning, neural networks, and natural language processing.

- **Machine Learning (ML):** an AI technique "*that can be used to design and train software algorithms to learn from and act on data*." Algorithm can be 'locked' so that its function does not change, or 'adaptive' so its behavior can change over time based on new data.

Example AI term in digital pathology: computer-aided detection/diagnosis

https://www.fda.gov/medical-devices/digital-health/digital-health-criteria

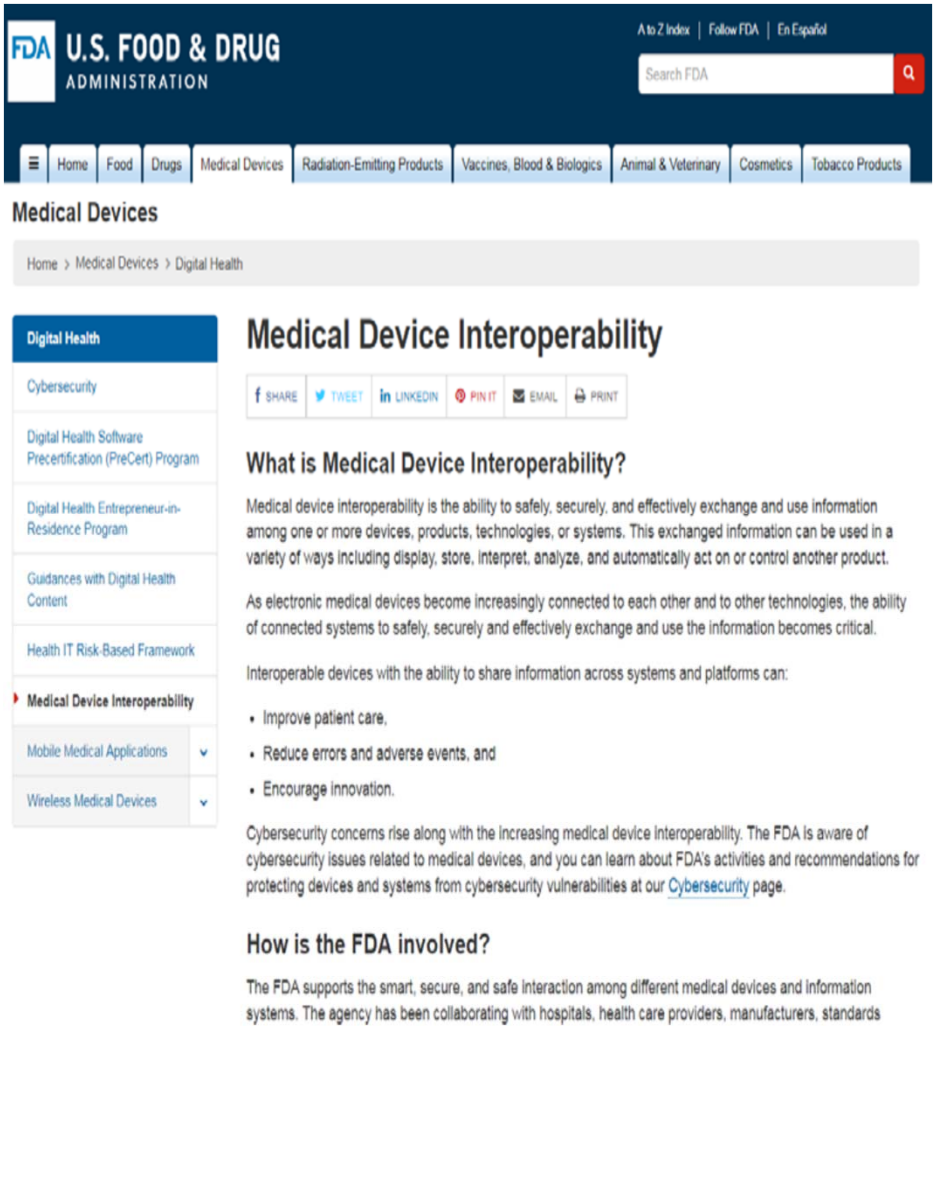
Software as a Medical Device (SaMD)

- SaMDs are software intended to be used for medical purposes such as “treat, diagnose, cure, mitigate, or prevent disease or other conditions” without being part of a hardware medical device.

[The Federal Food, Drug, and Cosmetic Act (FD&C Act)]

- AI/ML based devices are SaMD type devices, however……
  - They have the potential to adapt, optimize and continuously improve device performance in real-world setting

Medical Device Interoperability



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- Digital Health Entrepreneur-in-Residence Program
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- Health IT Risk-Based Framework
- Medical Device Interoperability
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Medical Device Interoperability

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What is Medical Device Interoperability?

Medical device interoperability is the ability to safely, securely, and effectively exchange and use information among one or more devices, products, technologies, or systems. This exchanged information can be used in a variety of ways including display, store, interpret, analyze, and automatically act on or control another product.

As electronic medical devices become increasingly connected to each other and to other technologies, the ability of connected systems to safely, securely and effectively exchange and use the information becomes critical.

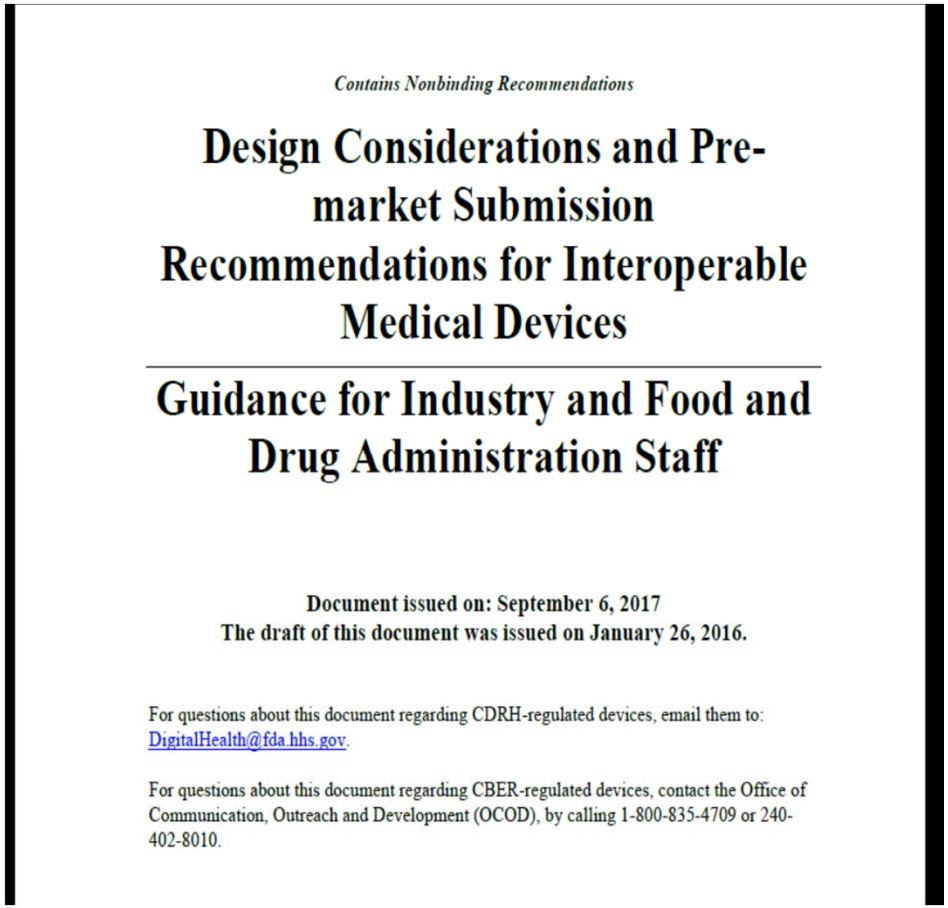
Interoperable devices with the ability to share information across systems and platforms can:

- Improve patient care,
- Reduce errors and adverse events, and
- Encourage innovation.

Cybersecurity concerns rise along with the increasing medical device interoperability. The FDA is aware of cybersecurity issues related to medical devices, and you can learn about FDA's activities and recommendations for protecting devices and systems from cybersecurity vulnerabilities at our Cybersecurity page.

How is the FDA involved?

The FDA supports the smart, secure, and safe interaction among different medical devices and information systems. The agency has been collaborating with hospitals, health care providers, manufacturers, standards



Contains Nonbinding Recommendations

Design Considerations and Pre-market Submission Recommendations for Interoperable Medical Devices

Guidance for Industry and Food and Drug Administration Staff

Document issued on: September 6, 2017
The draft of this document was issued on January 26, 2016.

For questions about this document regarding CDRH-regulated devices, email them to: DigitalHealth@fda.hhs.gov.

For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach and Development (OCOD), by calling 1-800-835-4709 or 240-402-8010.

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Digital Health: Current FDA Efforts

- Fostering collaborations and enhancing outreach to digital health customers
  - ties into CDRH initiative "Collaborative Communities"

- Developing and implementing regulatory strategies and policies for digital health technologies
  - "Proposed Regulatory Framework for Modifications to AL/ML based SaMDs" – FDA white paper

Collaborative Communities

- Part of CDRH strategic objectives
- The communities are “forums where public and private stakeholders work together to overcome medical device challenges and achieve common objectives.”
- To consider and integrate input by collaborating with stakeholders throughout the device ecosystem
- Has particular relevance to AI/ML based digital pathology devices

Proposed Regulatory Framework – FDA White Paper

On April 2, 2019, the FDA published the above discussion paper

It describes the FDA's foundation for a potential approach to premarket review for artificial intelligence and machine learning-driven software modifications.

Proposed General Approaches

The proposed general regulatory approach is based on the following:

- IMDRF*'s risk categorization principles
- FDA's benefit-risk framework
- Risk management principles described in the software modifications guidance
- Organization-based total product lifecycle

*International Medical Device Regulators Forum

Proposed General Regulatory Framework

Predetermined "change control plan" to be submitted in premarket submissions

- This plan would include the types of anticipated modifications referred to as the "Software as a Medical Device Pre-Specifications", and

- The associated methodology being used to implement those changes referred to as the "Algorithm Change Protocol"

  Changes should be implemented in a controlled manner that manages risks to patients

Proposed General Regulatory Framework – Cont'd

In this approach, the FDA would expect

- Commitment from manufacturers on transparency and real-world performance monitoring for AI/ML based software as a medical device

- Periodic updates to the FDA on what changes were implemented as part of the approved pre-specifications and the algorithm change protocol

Proposed General Regulatory Framework – Cont'd

Potential benefits from the proposed regulatory framework

- Could enable FDA and manufacturers to evaluate and monitor a software product from its premarket development to post-market performance

- Enables FDA's regulatory oversight to include the iterative improvement power of AI/ML based software as a medical device, while assuring patient safety

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AI in Digital Pathology: Regulatory Considerations

- Risk-based approach: Anticipate De Novo regulatory pathway if device is not high risk
- Type of AI algorithm: Locked vs. Adaptive
- Intended use (IU)
  - Concurrent review
  - In addition to standard of care review
  - Replaces standard of care
- Where does the AI device fit in the intended use workflow
- Currently, AI applications in digital pathology are mainly image-based, i.e. digital images of scanned glass slides. Therefore, differences in AI device performance based on differences in digital images should be assessed

AI in Digital Pathology: Regulatory Considerations

Performance Assessment:

- Description of the AI algorithm development and training prior to analytical and clinical validation. Has bias been adequately addressed?
- Standalone performance assessment – Precision/accuracy
- Other analytical performance studies, as applicable
- Validation study (clinical study) - example
  - Algorithm locked prior to clinical study
  - Assess performance without and with the aid of the device
  - Multiple clinical study sites, multiple pathologists, adequate sample size
  - Pre-defined inclusion/exclusion criteria
  - Study population representative of the IU population in terms of demographic/clinical characteristics and disease spectrum
  - Pre-specified performance metrics and goals

AI in Digital Pathology: Regulatory Considerations

After marketing authorization……

- How to monitor device performance after marketing authorization?
- Will the AI device have different performance based on the individual laboratories (continuous learning based on different inputs)?
- Will the AI device have the same performance on the same set of samples after "continuous learning" in post market setting?
- What is the level of "learning" after which an AI device should be considered as "new" device?
- Is it possible for AI devices to identify new pathology diagnostic entities or new reporting criteria? How to handle change in standard of care based on AI device performance in real-world?
- A protocol to specify how the software will be updated and when a premarket application is required for the changes

Questions?

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