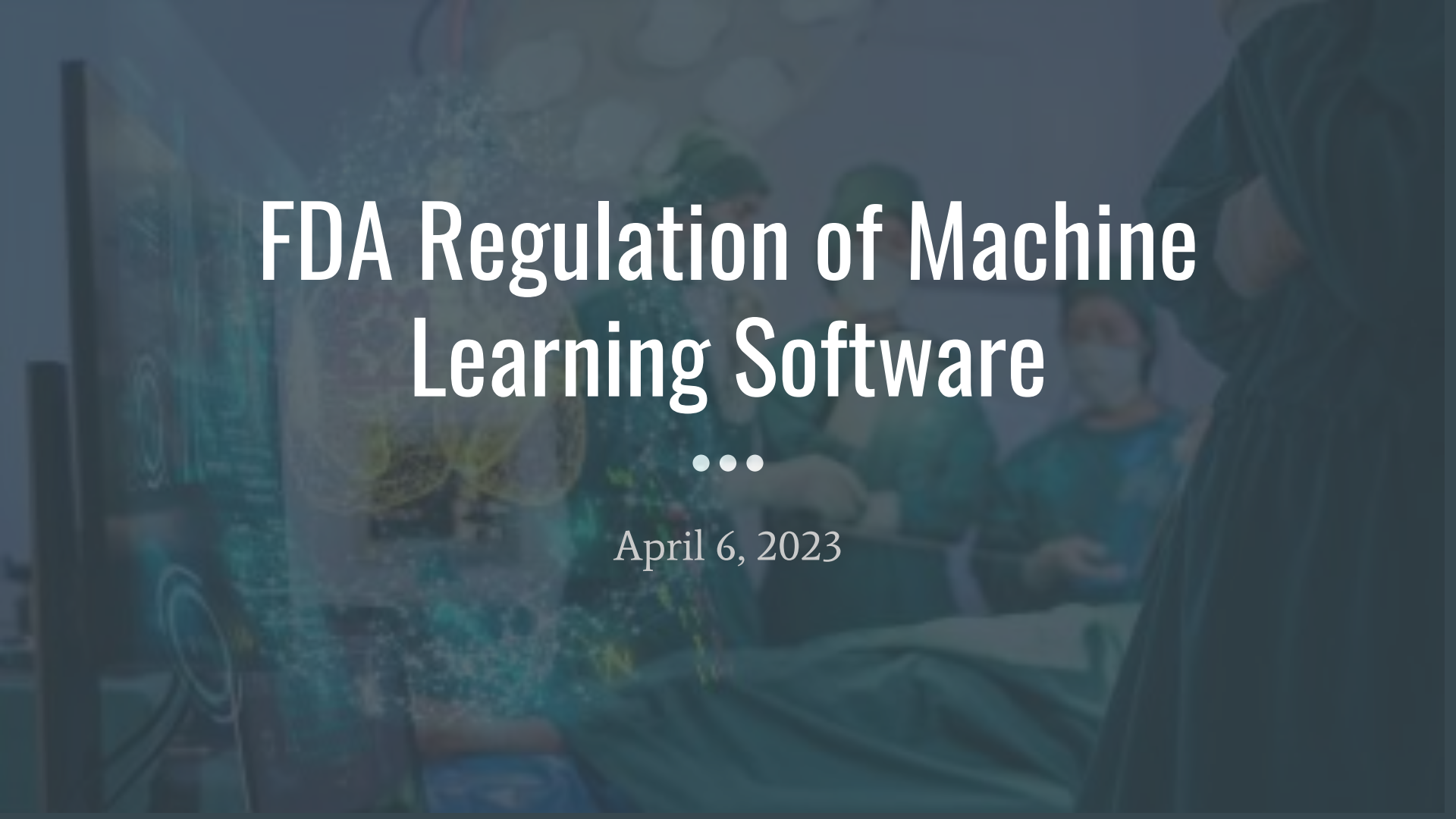


FDA Regulation of Machine Learning Software

April 6, 2023

What’s the FDA?

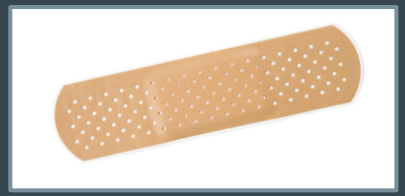
FDA

Food and Drug Administration

What does it regulate?

1. Food
2. Drugs
3. Cosmetics
4. Medical Devices

What’s a medical device?




PULL
Call 911
HEARTSTART
DEFIBRILLATOR
PHILIPS


Hot & Cold
Therapy Gel Pack
Freezable • Microwavable • Reusable

1. An instrument, apparatus, implement, machine, etc.
2. which is used to diagnose, prevent, or treat a medical disease or condition
3. without having any chemical action on any part of the body

How are medical devices regulated?

Class I:	**Class II:**	**Class III:**
Minimal risk to patient	Important, but unlikely to cause critical harm to patient	**Implanted or life-sustaining devices, problems could lead to significant adverse outcome to patient**

• General controls
  ○ 510(k) registration
	• General controls
	  ○ 510(k) registration
	• Special controls
		• General controls
		• Premarket approval

• Qtips • Dental floss • Wheelchairs	• Contact lenses • Catheters • Pregnancy test kits	• Pacemakers • Cochlear implants • Defibrillators

General controls

- Apply to all 3 medical device classes
- Broad requirements that aim to foster safe and effective medical devices, include:
  - Establishment registration
    - Establishments must register their medical device with the FDA annually - $6,493/yr
  - Device reporting
    - establishments must report device-related injuries and deaths to FDA
  - Good manufacturing practices
    - minimum requirements for the methods, facilities, and controls used in designing, manufacturing, packaging, labeling, storing, installing, and servicing medical devices

Special controls

- Apply to Class II medical devices only
- General controls alone are insufficient to provide reasonable assurance of the safety and effectiveness of the device
- Vary depending on type of device - specific requirements applied to well-established device types
- Include:
  - Special labeling requirements
  - Performance standards
  - Patient registries

510(k) premarket notification

- Some Class I devices and most Class II devices are also subject to 510(k) premarket notification - around $20,000 ($5,000 if small business)
- The submitter must compare their device to a legally marketed device (“predicate”) and demonstrate how it is substantially equivalent
- Substantial equivalence means that the new device is just as safe and effective as the predicate
    - Must have the same intended use, and
    - Has the same technological characteristics, OR
    - Has different technological characteristics but is shown to have the same safety and effectiveness as the predicate
- Substantial changes to a Class II medical device require a new 510(k)

Premarket approval

- All Class III devices are subject to premarket approval - $442,000 ($110,000 if small business)
- FDA determines whether there is sufficient scientific evidence to ensure the device is safe and effective for its intended user(s)
- Substantial changes to a Class III medical device require new premarket approval

Medical devices & software

1. the software that makes the MRI machine run
2. the software that analyzes the images of the MRI

Software in a Medical Device (SiMD)

- software that is part of another medical device and helps it function in some way

Software as a Medical Device (SaMD)

- software that is itself a medical device, and functions completely independently of existing medical devices
- AI and machine learning SaMD has gained popularity recently

The FDA's Proposed Regulatory Framework

- Because machine learning SaMD has gained popularity, the FDA has been considering new ways to regulate these kinds of medical devices, particularly device modifications
- What are the issues that arise from modifications to machine learning SaMD?

Total product lifecycle (TPLC) regulatory approach

1. Establish good machine learning practices (GMLP)
2. Conduct premarket review to demonstrate reasonable assurance of safety, and continually manage patient risks throughout lifecycle
3. Expect manufacturers to monitor the device for risk in the development, validation, and execution of algorithm changes
4. Enable increased transparency to users and FDA using postmarket real-world performance reporting for maintaining continued assurance of safety and effectiveness

Good Machine Learning Practices

- Machine learning algorithm development involves learning from data - what considerations are important here?

GLMP:

1. Data should be relevant to the clinical problem
2. Data should be acquired in a consistent and clinically relevant manner
3. There should be appropriate separation between training, tuning, and test datasets
4. There should be an appropriate level of transparency of the output aimed at users

Premarket assurance of safety and effectiveness

- Manufacturers have the option to submit a plan for modifications during the initial premarket review (“predetermined change control plan”)
    1. SaMD pre-specifications - types of anticipated modifications
    2. Algorithm change protocol - methodology being used to implement those changes in a controlled manner that manages risks to patients

Predetermined change control plan

SaMD Pre-Specifications

- What type of change do you anticipate?
  - Performance
  - Inputs
  - Intended use

Algorithm Change Protocol

- How will the algorithm learn and change while remaining safe and effective?
  - Data management
  - Re-training
  - Performance evaluation
  - Update procedures

Types of modifications

1. Performance - sensitivity, specificity
    a. increased sensitivity of a software at detecting lesions suspicious for cancer
2. Inputs
    a. software modification to support compatibility with CT scanners from additional manufacturers
    b. expanding the types of data used by the software (temperature data in addition to visual data)
3. Intended use
    a. change in the significance of information provided by the software - from aiding in diagnosis to actually providing a diagnosis
    b. expand intended patient population or change user base - from adults to children

IMDRF Risk Categorization

State of healthcare situation or condition	Significance of information provided by SaMD to healthcare decision		
	treat or diagnose	drive clinical management	inform clinical management
critical	IV	III	III
serious	III	II	I
non-serious	II	I	I

example

Ted creates a SaMD app that uses images taken by a smartphone camera to provide detailed information to a dermatologist on the physical characteristics of a skin lesion in order for the dermatologist to label the skin lesion as benign or malignant.

Risk categorization:

- drive clinical management in a serious healthcare situation → level II

example cont...

Ted decides to submit a predetermined change control plan.

- SPS: he anticipates a potential modification allowing for increased sensitivity and specificity in analyzing the physical characteristics of lesions using real-world data
    - Q: what type of modification would this be - performance, input, or intended use?
- ACP: includes detailed methods for database management, retraining, evaluating performance, and updates

example cont...

Down the line, Ted implements a modification consistent with his predetermined change control plan.

- He collected real-world data from use of the app on various smartphone platforms. This improved sensitivity and specificity in assessment of skin lesion physical characteristics as described in his plan.
- Result: the modified algorithm that 'learned' on real-world data can probably be marketed without additional FDA review.

example cont...

Later, Ted wants to make a version of his app that is patient-facing. This version would provide an analysis of the physical characteristics of skin lesions, as it does currently, and direct patients to follow-up with a dermatologist based on the preliminary analysis of the malignancy of the skin lesion.

Do you think this introduces new risks to patients?

- Probably, yes.
- So - the FDA may require a new pre-market submission for this modification

Takeaways

- Modifications to SaMD that significantly increase the risk to patients will probably require a new pre-market submission
- This is all proposed
- FDA next steps:
  - Just released a new guidance document
  - Comments open through July 3rd

questions?