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Evaluation and Regulatory Considerations for AI Methods in Medical Imaging

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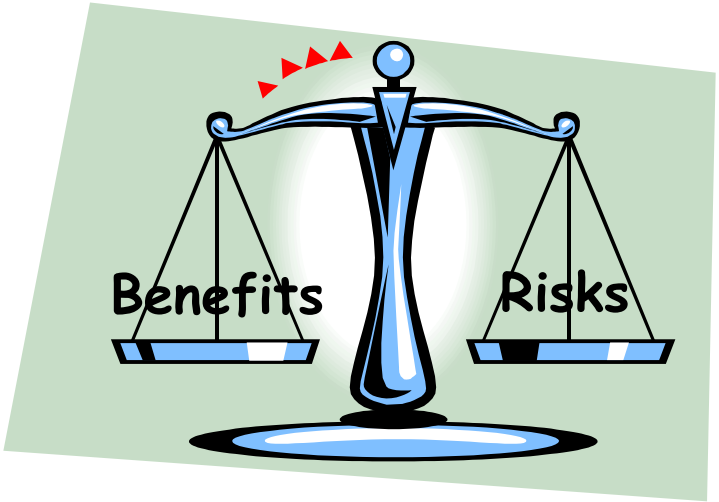
US Food and Drug Administration

CDRH/OSEL

Division of Imaging, Diagnostics and Software Reliability

Center for Devices and Radiological Health

- Protect and promote the health of the public by ensuring the safety and effectiveness of medical devices and the safety of radiation-emitting electronic products



Division of Imaging, Diagnostics and Software Reliability

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- Part of Office of Science and Engineering Labs within CDRH
- Support the mission the through investigating issues related to
  - Medical imaging
  - Computer-assisted diagnosis
  - Software reliability
- Major research effort related to assessment of AI/ML systems
- Website: Search for FDA DIDSR

PI Name	Project Title
Weijie Chen	Technical and statistical assessment of AI/ML in digital pathology for clinical deployment
Brandon Gallas	High-throughput truthing of microscope slides to validate artificial intelligence algorithms analyzing digital scans of same slides
Marios Gavrielides	Improving pathologist performance for diagnosis of ovarian cancer histological subtypes using machine learning tools
Stephen Glick	Development of a deep learning model observer to assess performance of x-ray breast imaging systems
Aria Pezeshk	Recurrent conv. networks for nodule detection in thoracic CT scans
A. Pezeshk and Christian Graff	Comparison of quality assessment methods for deep-learning-based MR image reconstruction
Aria Pezeshk	Assessment of AI systems that use un-annotated or weakly labeled datasets in training
B. Sahiner and Weijie Chen	Leveraging imperfect post-market reference indices for the evaluation of artificial intelligence and machine learning devices
B. Sahiner and Alexej Gossmann	Assessment of adaptive machine learning systems: Methods for re-use of holdout sets and application to deep learning systems for medical image
R. Zeng and Christian Graff	Deep learning-based image reconstruction and denoising in radiological imaging

What is a Medical Device?

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- 1938 Federal Food, Drug, and Cosmetic Act (FD&C Act):
  - "… an instrument, apparatus, …
  - **intended for use in the diagnosis of disease or other conditions**, or
  - **in the cure, mitigation, treatment or prevention of disease …**, or
  - **intended to affect the structure or any function of the body** …"
- If a product meets this definition, there are FDA regulatory requirements that must be met before it can be **marketed** in the U.S.

Medical Device Classification

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- Risk-based paradigm

Device Class	Controls	Premarket Review Process
Class I (lowest risk)	General Controls	Most are exempt
Class II	General Controls & Special Controls	Mostly Premarket Notification [510(k)]
Class III (highest risk)	General Controls & Premarket Approval	Mostly Premarket Approval [PMA]

Paths to Market with Premarket Review

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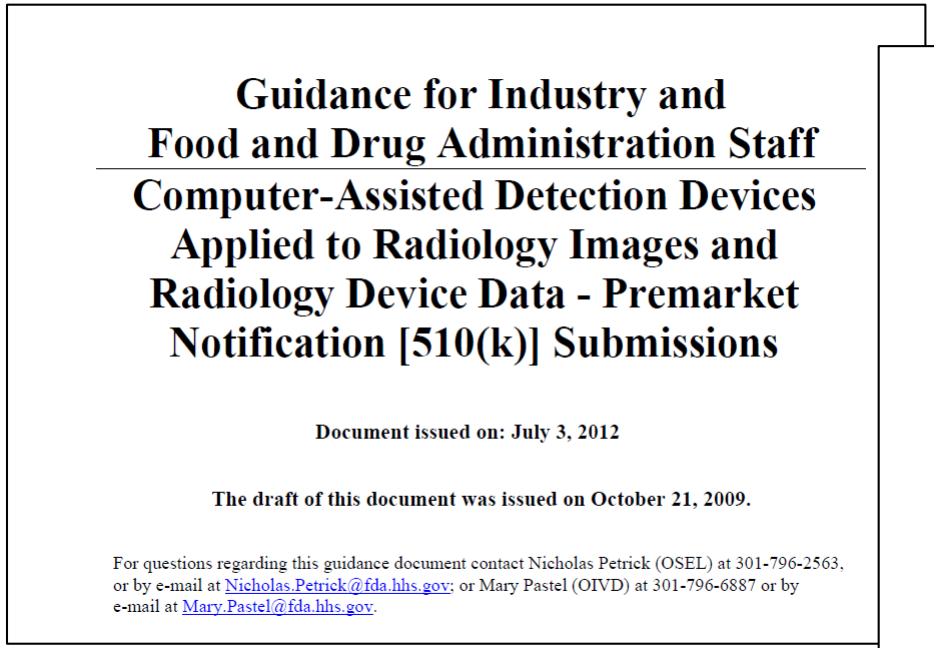
- 510(k) clearance: Typically Class II
  - Substantial equivalence to a legally marketed predicate device
- Pre-market approval: Typically Class III
  - Demonstration of reasonable assurance of safety and effectiveness of the subject device
- De-Novo
  - Petition for down classification, typically from Class III to Class II
  - A granted de novo establishes a new device type, a new device classification, a new regulation, and necessary general (and special) controls
  - Once the de novo is granted, the device is eligible to serve as a predicate
  - All the followers are 510(k) devices

Uses of AI/ML in Medical Image Analysis

- Image filtering and denoising
- Quantitative imaging
- Computer-aided detection (CADe)
  - First reader
  - Sequential reading
  - Concurrent reading
- Computerized detection
- Computer-aided diagnosis (CADx)
  - Presence/absence of disease
  - Severity, stage, prognosis, response to therapy
  - Recommendation for intervention
- Triage
- Many other possibilities

CADe Guidances



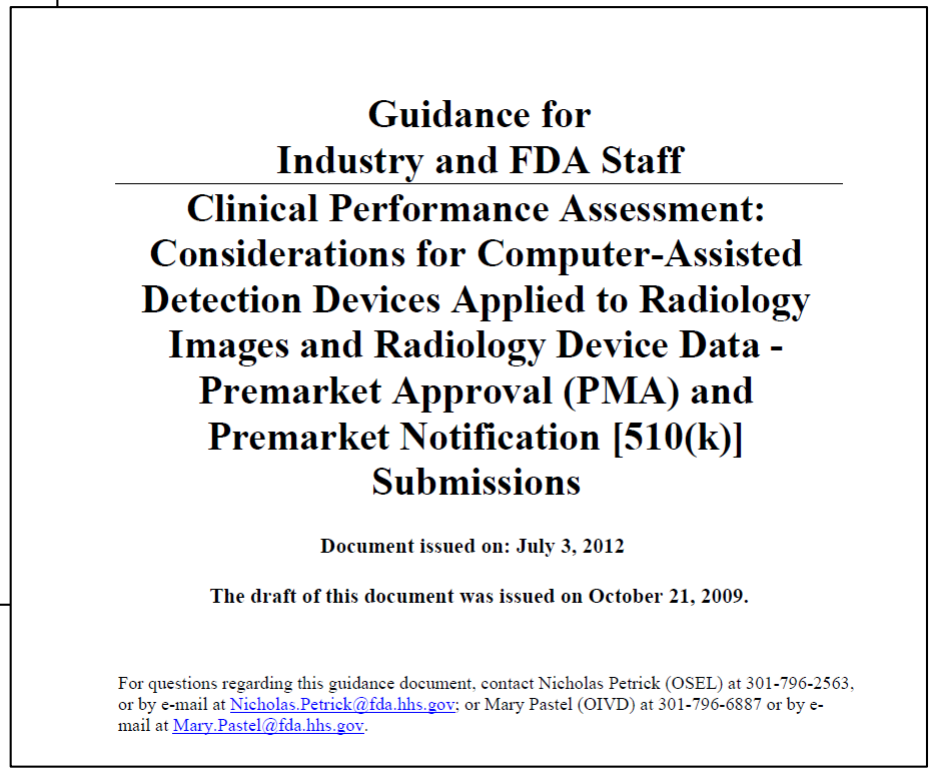
Guidance for Industry and Food and Drug Administration Staff

Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data - Premarket Notification [510(k)] Submissions

Document issued on: July 3, 2012

The draft of this document was issued on October 21, 2009.

For questions regarding this guidance document contact Nicholas Petrick (OSEL) at 301-796-2563, or by e-mail at Nicholas.Petrick@fda.hhs.gov; or Mary Pastel (OIVD) at 301-796-6887 or by e-mail at Mary.Pastel@fda.hhs.gov.



Guidance for Industry and FDA Staff

Clinical Performance Assessment: Considerations for Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data - Premarket Approval (PMA) and Premarket Notification [510(k)] Submissions

Document issued on: July 3, 2012

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Many New DeNovo Devices in the Past 2 Years

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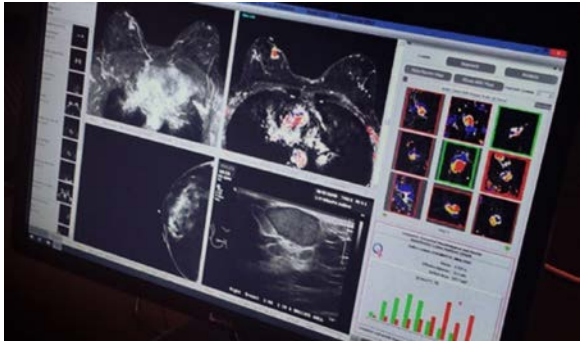
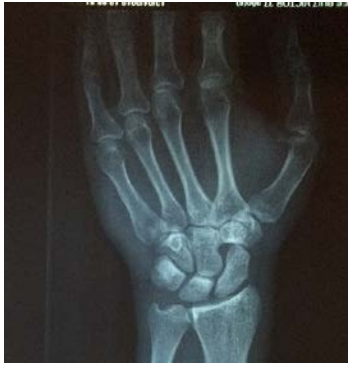
- Regulations mostly similar to CADe devices

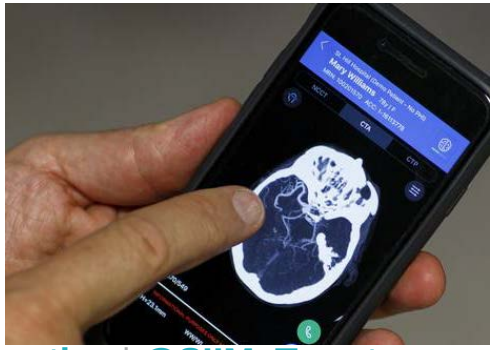
Computer-Aided Classification of Breast Lesions on Magnetic Resonance Imaging:
Computer-Aided Diagnosis (CADx)

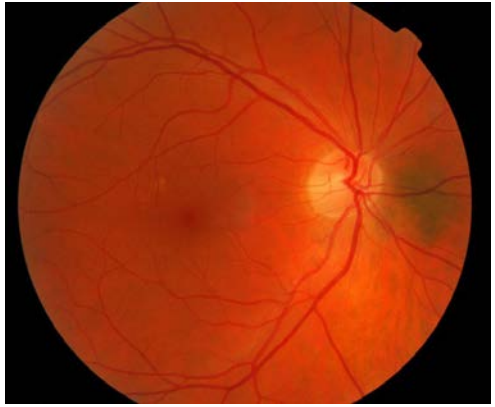




Computer-Aided Detection and Diagnosis of Fractures on Radiographs:
CADe + CADx

Notification of Specialists for Suspicion of Stroke on Computerized Tomography Images:
Radiological Computer Aided Triage





Detection of Diabetic Retinopathy on Retina Fundus Images:
Retinal Diagnostic Software

Software as a Medical Device (SaMD)

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- Software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device
  - Capable of running on general purpose (non-medical purpose) computing platforms
  - “Without being part of” means software not necessary for a hardware medical device to achieve its intended medical purpose
    - If it drives a hardware medical device, it is not SaMD

Software as a Medical Device (SAMD): Clinical Evaluation

Guidance for Industry and Food and Drug Administration Staff

Document issued on December 8, 2017.

The draft of this document was issued on October 14, 2016.

Fundamentals of AI/ML Based Image Analysis SaMD

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- Device description
- Data
- Performance assessment
  - Standalone performance
  - Reader performance (when appropriate)
  - …
- Human factors or other information/testing as appropriate
- …

Device Description

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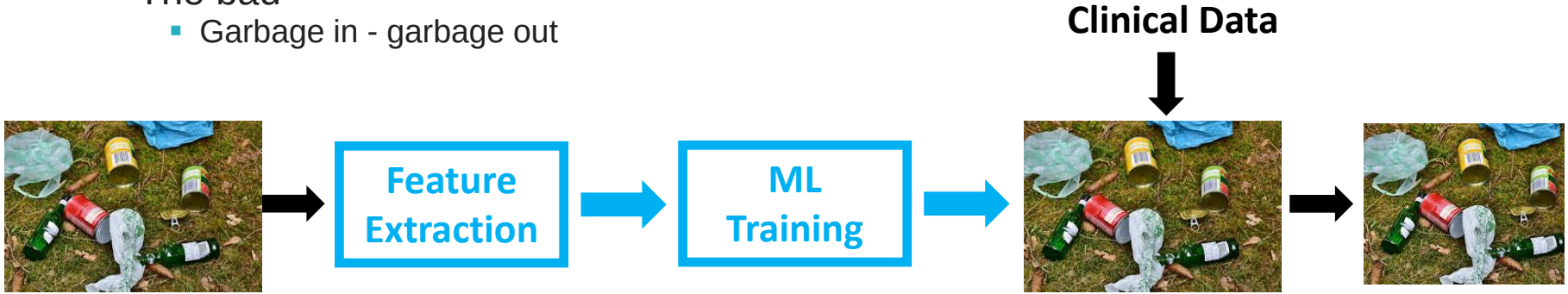
- Device & algorithm descriptions
  - Device usage (mode, of operation, patient population, …)
  - Algorithm design and function
    - Including structure of traditional and deep learning networks
    - Inputs
      - Type and range of signals/data
    - Outputs
  - Training process
  - Training/test database
  - Reference standard
  - …

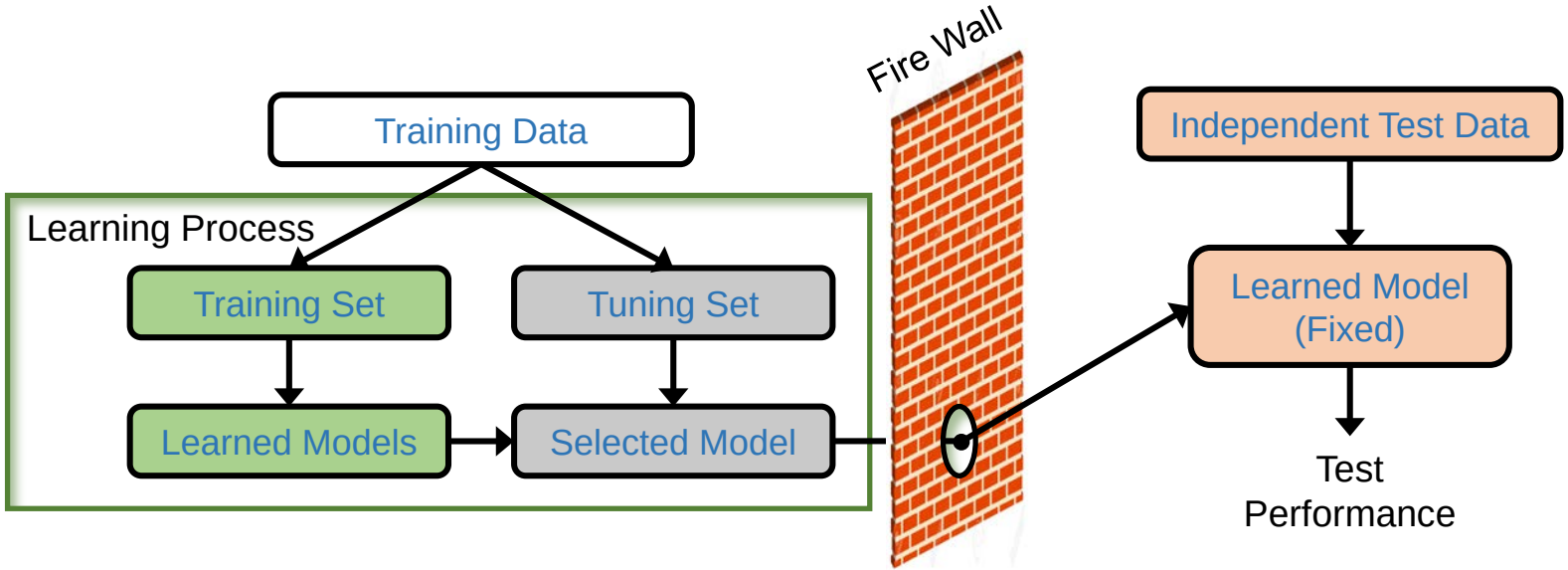
Data

- ML algorithms are data-driven
  - Versus, for example, physics or biology based
- ML algorithms development now facilitated by standardized ML platforms
  - Brings ML to a wider array of users
  - The good
    - Access to high-quality data streamlines design of novel ML applications
  - The bad
    - Garbage in - garbage out



Performance testing

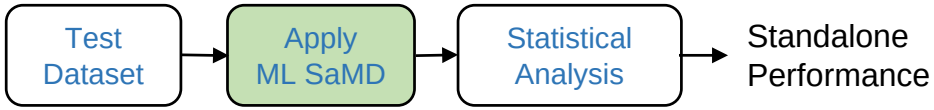
- Performance of ML algorithm on an independent data
  - Ideally, identifies problems with training process



Performance assessment

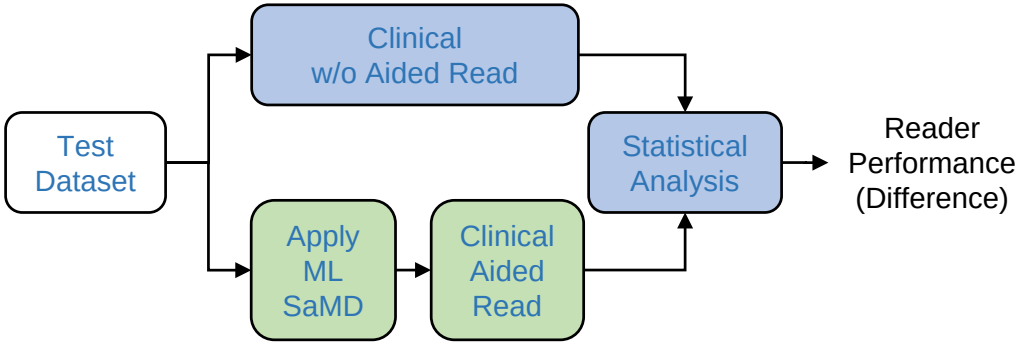
Standalone Performance

- Performance of algorithm alone
- Assesses robustness and generalizability of algorithm



Clinical reader performance

- Assessment of clinical aids
- Clinicians' performance utilizing device
  - Multi-reader multi-case designs
  - Compare clinician's performance with the ML SaMD aid to without the aid



An New Regulatory Challenge

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- Traditionally, algorithm changes that significantly affect the device's performance, would require a new submission to the FDA, as per the Software Modifications Guidance
- Ideally, devices incorporating ML keep learning after release
  - Ever enlarging data sets for algorithm training
  - New types of input
  - New architectures/models
- How can the FDA provide oversight to adapting devices in a manner that is aligned with the technology's lifecycle?

Proposed Regulatory Framework for Modifications to AI/ML Algorithms

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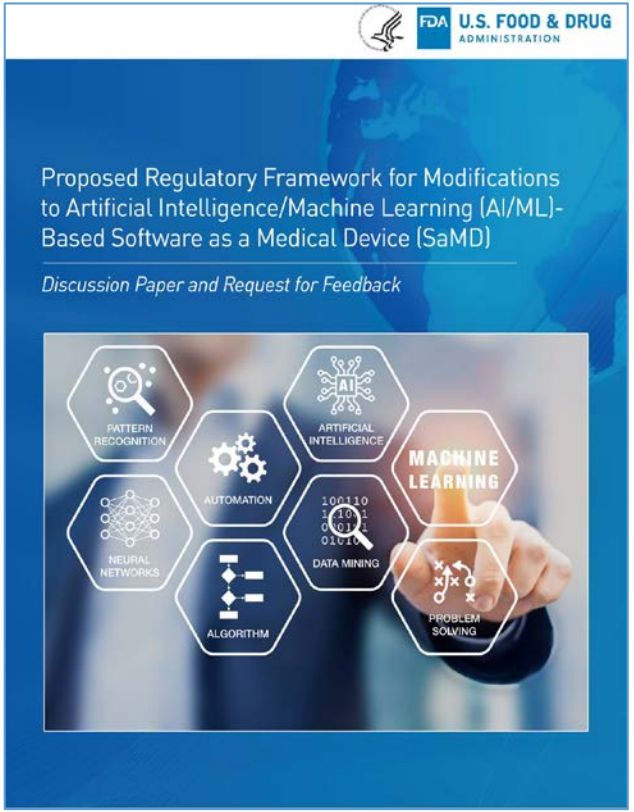
- An option to submit a plan for modifications during the initial premarket review of an AI/ML-based SaMD
- Reviewed during initial premarket phase
  - SaMD performance
  - Plan for modifications
  - Ability to manage/control resultant risks of modifications
- Comment period formally ended June 3rd



https://www.regulations.gov/document?D=FDA-2019-N-1185-0001

A Pre-Determined Change Control Plan

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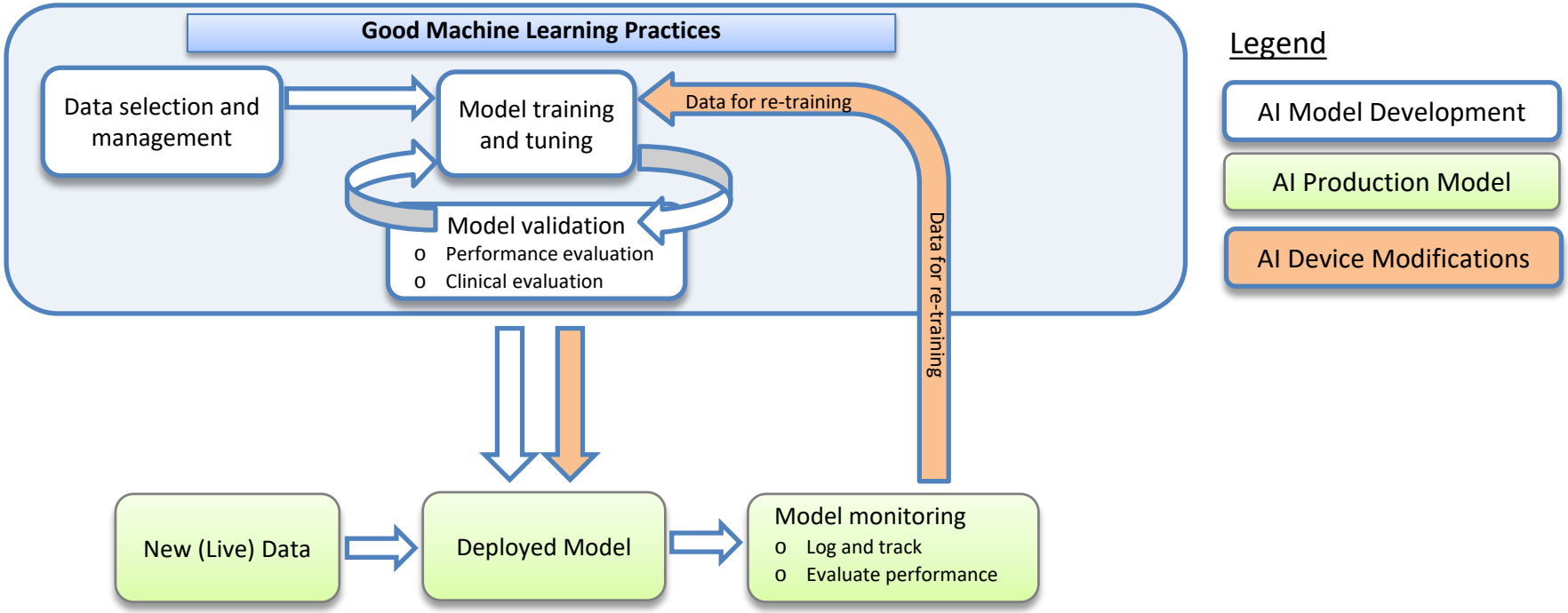
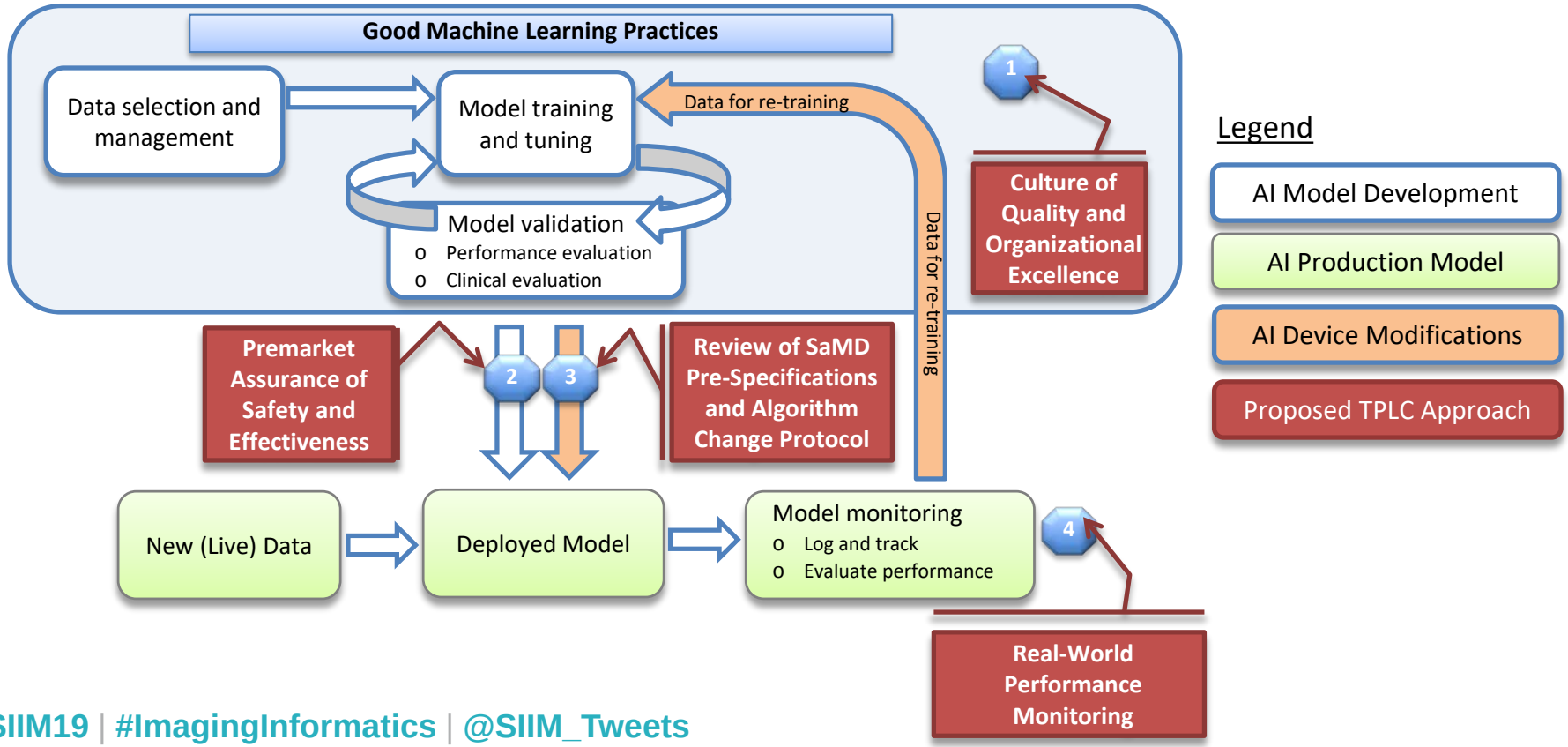
- SaMD Pre-Specifications (SPS):
  - Delineates the proposed types of modifications to the SaMD
    - What types of changes the does the sponsor plan to achieve
- Algorithm Change Protocol (ACP):
  - Describes the methods for performing and validating the changes pre-specified in SPS
    - How does the sponsor intend to achieve the changes
  - Typically specific to the device and type of change
  - Expected to contain a step-by-step delineation of the procedures to be followed
- Good ML Practices (GMLP):
  - Accepted practices in AI/ML algorithm design, development, training, and testing that facilitate the quality development and assessment of AI/ML-based algorithms
  - Based on concepts from quality systems, software reliability, machine learning, and data analysis, etc.

Current AI/ML Workflow



FDA's Proposed Approach



Software Precertification Pilot Program

- Voluntary pathway
- Streamlined and efficient regulatory oversight of software based-medical devices for manufacturers who demonstrate
  - Robust culture of quality
  - Organizational excellence (CQOE)
  - Commitment to monitoring real-world performance
- Latest working model: v1.0 Jan. 2019
  - https://www.fda.gov/media/119722/download
- Continue to build and refine the current working model

Total Product Lifecycle Approach of the Software Pre-Cert Program

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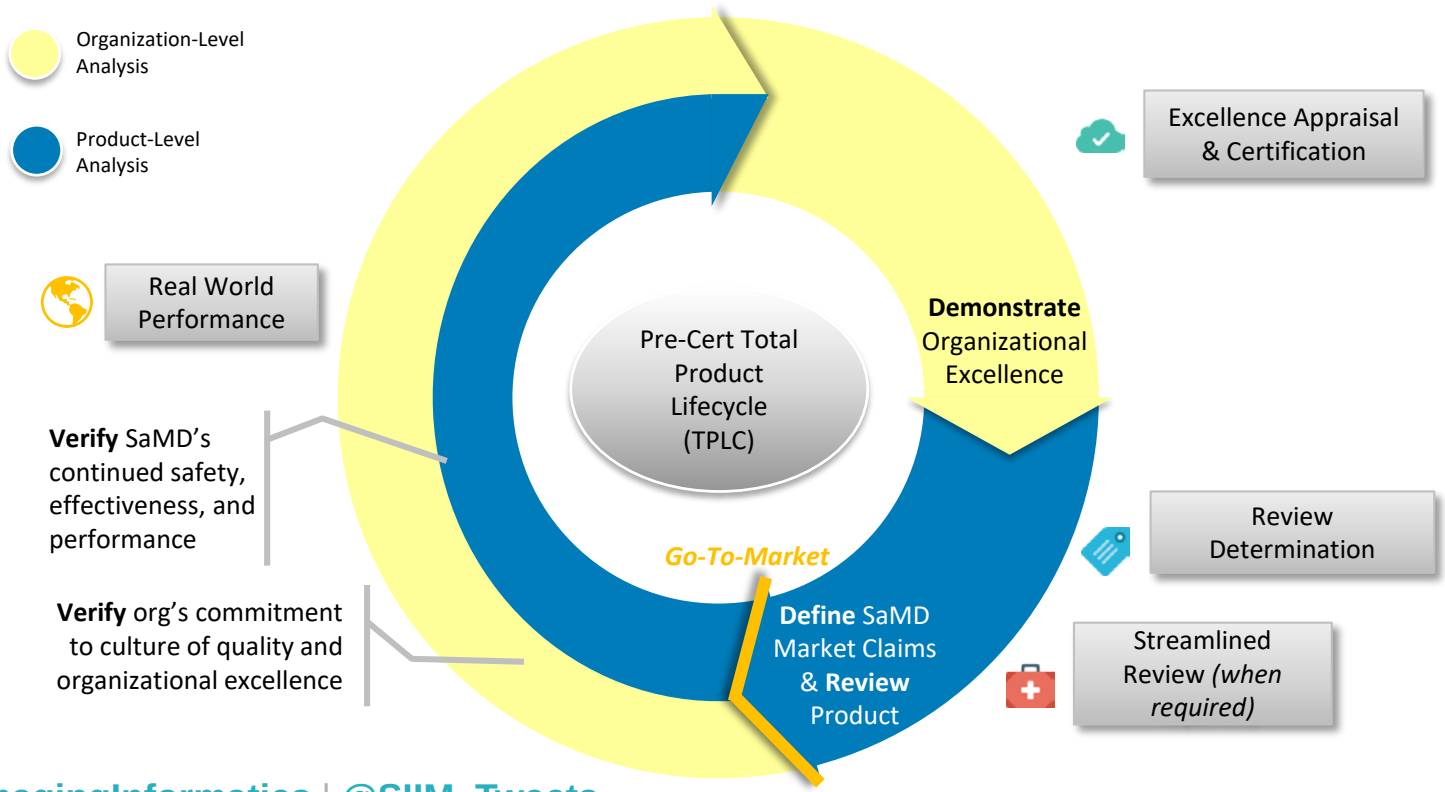

Relevant Guidances, Regulations and Discussion Papers

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Guidances

- CADe: http://www.fda.gov/RegulatoryInformation/Guidances/ucm187249.htm
  http://www.fda.gov/RegulatoryInformation/Guidances/ucm187277.htm
- SaMD evaluation: https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm524904.pdf

Draft guidances and discussion papers

- Quantitative Imaging: https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM636178.pdf
- Modifications to AI/ML Software https://www.regulations.gov/document?D=FDA-2019-N-1185-0001

Regulations/reclassification orders

- CADx: https://www.accessdata.fda.gov/cdrh_docs/pdf17/den170022.pdf
- CADx+CADe: https://www.accessdata.fda.gov/cdrh_docs/pdf18/DEN180005.pdf
- Triage: https://www.accessdata.fda.gov/cdrh_docs/pdf17/DEN170073.pdf
- Retinal diagnosis: https://www.accessdata.fda.gov/cdrh_docs/pdf18/DEN180001.pdf

Summary

- AI/ML Software as a Medical Device review
  - FDA has substantial guidance on ML SaMD assessment
  - A number of DeNovo devices for image analysis that use machine learning
    - Opens the path for similar devices through 510(k) pathway
  - FDA's approach to SaMD is evolving
    - Precertification of organizations
    - Streamlining review processes for updates to ML SaMD
- AI/ML device assessment considerations
  - Data
    - Source, patient population, reference standard, …
  - Performance testing
    - Standalone testing
    - Reader performance assessment (when appropriate)
  - …

Acknowledgements

- Drs. Nick Petrick and Matthew Diamond contributed substantially to the preparation of this presentation