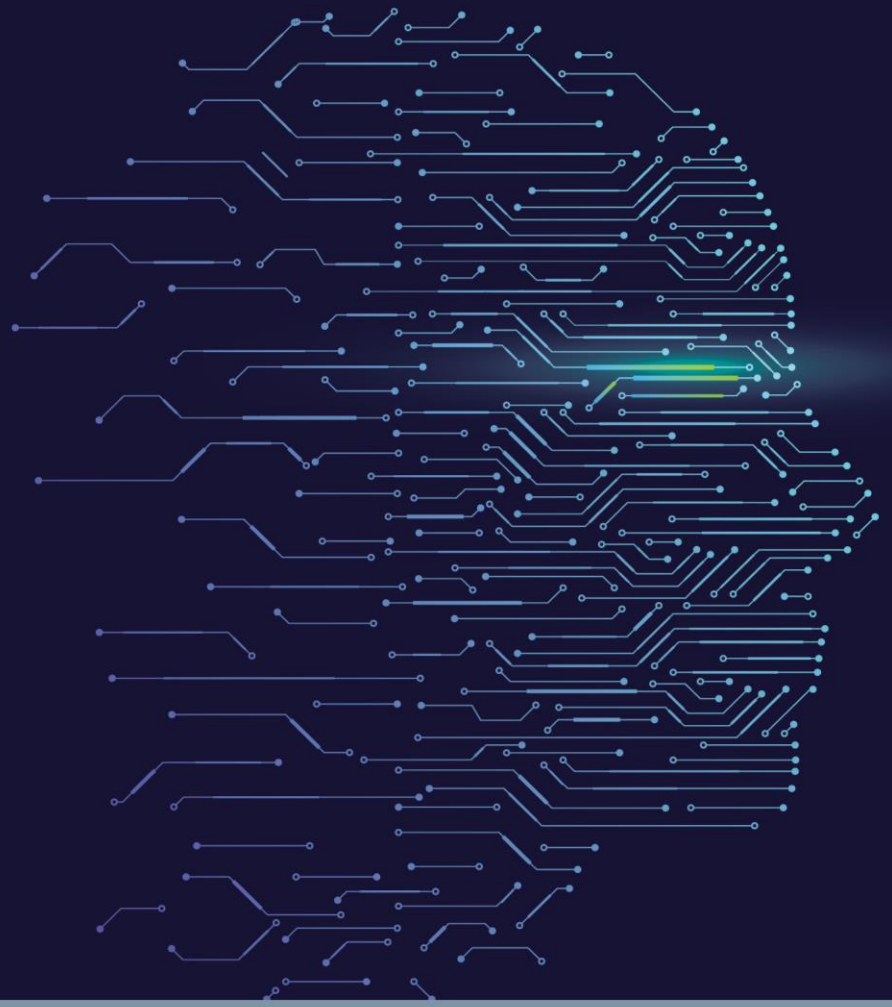
2019 IMAGING INFORMATICS SUMMIT



Evaluating Artificial Intelligence Devices at the FDA and Related Collaborations and Initiatives

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Jennifer Segui, Lead Medical Device Reviewer, Division of Radiological Health, FDA

ACR® American College of Radiology

WASHINGTON

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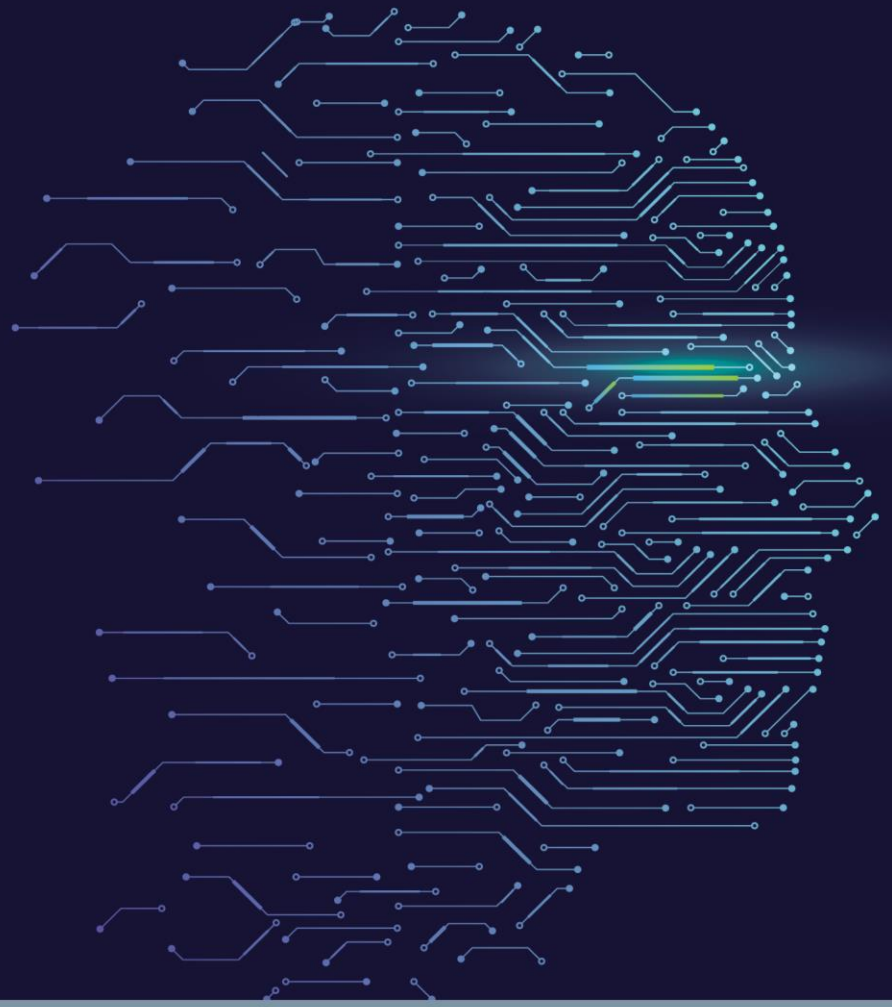


Part I. Definitions, Regulatory Review Process, and Tips for a Successful Premarket Submission

Jennifer Segui, Lead Medical Device Reviewer, Division of Radiological Health, FDA

ACR® American College of Radiology

WASHINGTON

Disclosures

- Jennifer Segui
  - My family includes a full-time employee at Glaxo Smith Kline (GSK)

Learning Objectives

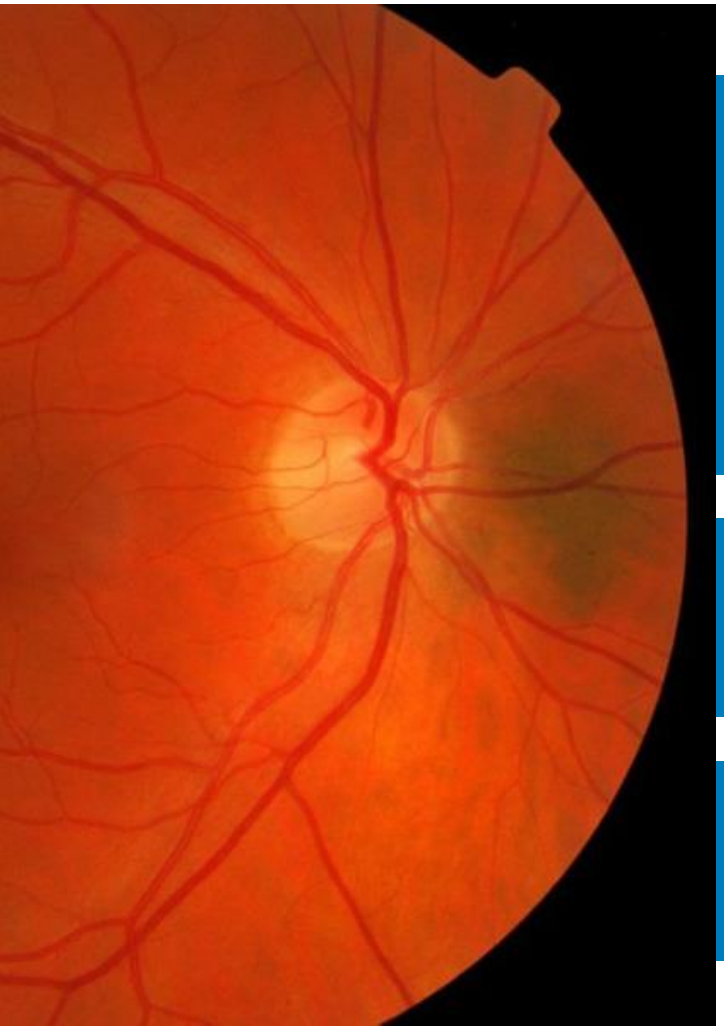
- Gain familiarity with the classifications and intended use of radiological imaging software reviewed within the Division of Radiological Health (CDRH/OPEQ/OHT7/DRH)
- Learn about the FDA regulatory review process including submission types
- Understand the role of substantial equivalence and benefit-risk in regulatory review and decision-making
- Discuss strategies for gaining approval for new, higher risk devices including AI-assisted radiology
- Discuss common issues in radiological imaging software submissions
- Improve awareness of FDA-led initiatives and other collaborations

Presentation Outline

- Artificial Intelligence in Medical Devices including Software as a Medical Device (SAMD)
- Devices Reviewed within the Division of Radiological Health
- Regulatory Review Objectives and Pathways
- Emerging Applications of AI/ML in Radiology with Tips for a Successful Submission
- Additional Resources

AI/ML Based Medical Devices

IDx-DR



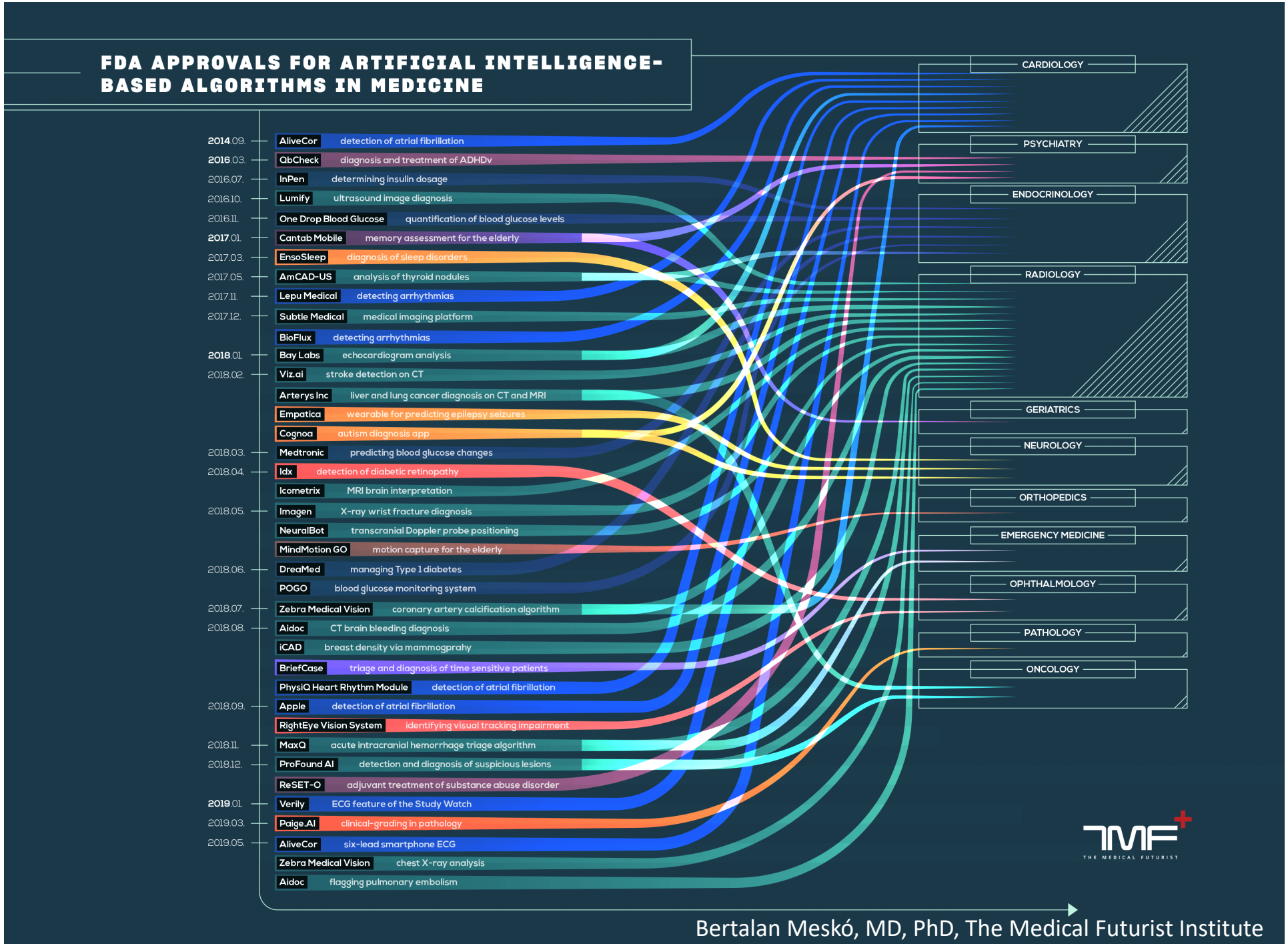
Potential to fundamentally transform the delivery of health care:

E.g., Earlier disease detection, more accurate diagnosis, new insights into human physiology, personalized diagnostics and therapeutics

Ability for AI/ML to learn from the wealth of real-world data and improve its performance

Already seen AI/ML lead to the development of novel medical devices

www.fda.gov/digitalhealth

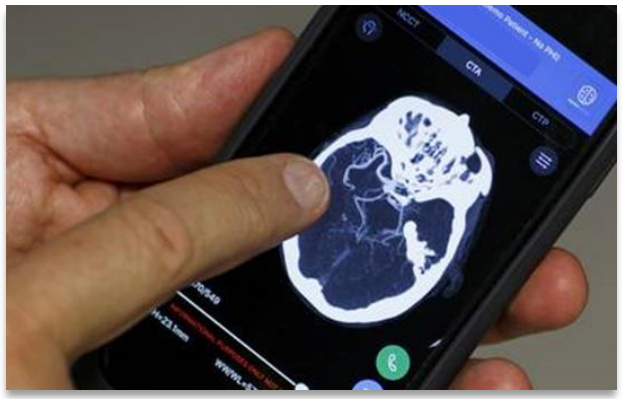

FDA APPROVALS FOR ARTIFICIAL INTELLIGENCE-BASED ALGORITHMS IN MEDICINE
2014.09. AliveCor detection of atrial fibrillation
2016.03. QbCheck diagnosis and treatment of ADHDv
2016.07. InPen determining insulin dosage
2016.10. Lumify ultrasound image diagnosis
2016.11. One Drop Blood Glucose quantification of blood glucose levels
2017.01. Cantab Mobile memory assessment for the elderly
2017.03. EnsoSleep diagnosis of sleep disorders
2017.05. AmCAD-US analysis of thyroid nodules
2017.11. Lepu Medical detecting arrhythmias
2017.12. Subtle Medical medical imaging platform
BioFlux detecting arrhythmias
2018.01. Bay Labs echocardiogram analysis
2018.02. Viz.ai stroke detection on CT
Arterys Inc liver and lung cancer diagnosis on CT and MRI
Empatica wearable for predicting epilepsy seizures
Cognoa autism diagnosis app
2018.03. Medtronic predicting blood glucose changes
2018.04. Idx detection of diabetic retinopathy
Icometrix MRI brain interpretation
2018.05. Imagen X-ray wrist fracture diagnosis
NeuralBot transcranial Doppler probe positioning
MindMotion GO motion capture for the elderly
2018.06. DreaMed managing Type 1 diabetes
POGO blood glucose monitoring system
2018.07. Zebra Medical Vision coronary artery calcification algorithm
2018.08. Aidoc CT brain bleeding diagnosis
iCAD breast density via mammogprahy
BriefCase triage and diagnosis of time sensitive patients
PhysiQ Heart Rhythm Module detection of atrial fibrillation
2018.09. Apple detection of atrial fibrillation
RightEye Vision System identifying visual tracking impairment
2018.11. MaxQ acute intracranial hemorrhage triage algorithm
2018.12. ProFound AI detection and diagnosis of suspicious lesions
ReSET-O adjuvant treatment of substance abuse disorder
2019.01. Verily ECG feature of the Study Watch
2019.03. Paige.AI clinical-grading in pathology
2019.05. AliveCor six-lead smartphone ECG
Zebra Medical Vision chest X-ray analysis
Aidoc flagging pulmonary embolism
CARDIOLOGY
PSYCHIATRY
ENDOCRINOLOGY
RADIOLOGY
GERIATRICS
NEUROLOGY
ORTHOPEDICS
EMERGENCY MEDICINE
OPHTHALMOLOGY
PATHOLOGY
ONCOLOGY
THE MEDICAL FUTURIST
Bertalan Meskó, MD, PhD, The Medical Futurist Institute

Examples of AI/ML-Based SAMD @ FDA

FDA News Release

FDA permits marketing of clinical decision support software for alerting providers of a potential stroke in patients

February 13, 2018



Viz.Ai

FDA News Release

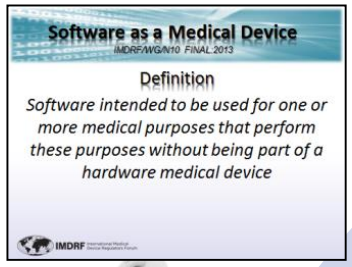
FDA permits marketing of artificial intelligence-based device to detect certain diabetes-related eye problems

April 11, 2018

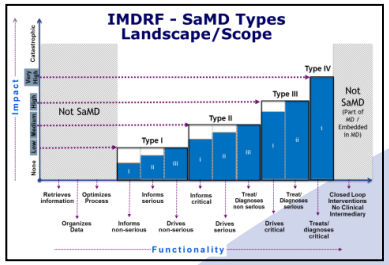
IDx-DR

IMDRF – toward global convergence in characterizing SAMD

Software as a Medical Device (SaMD)
Software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device

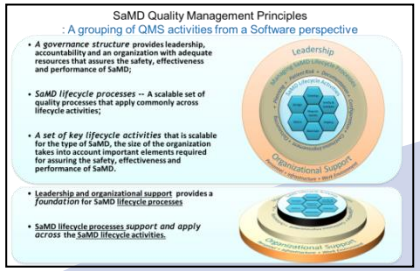


2013
Foundational vocabulary



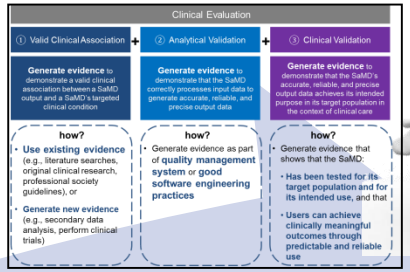
2014 –

Risk framework based on impact to patients



2015 –

QMS control
➔Translating Software development practices to regulatory QMS



2017 – SaMD Clinical Evaluation
➔Generating evidence for clinically meaningful SaMD

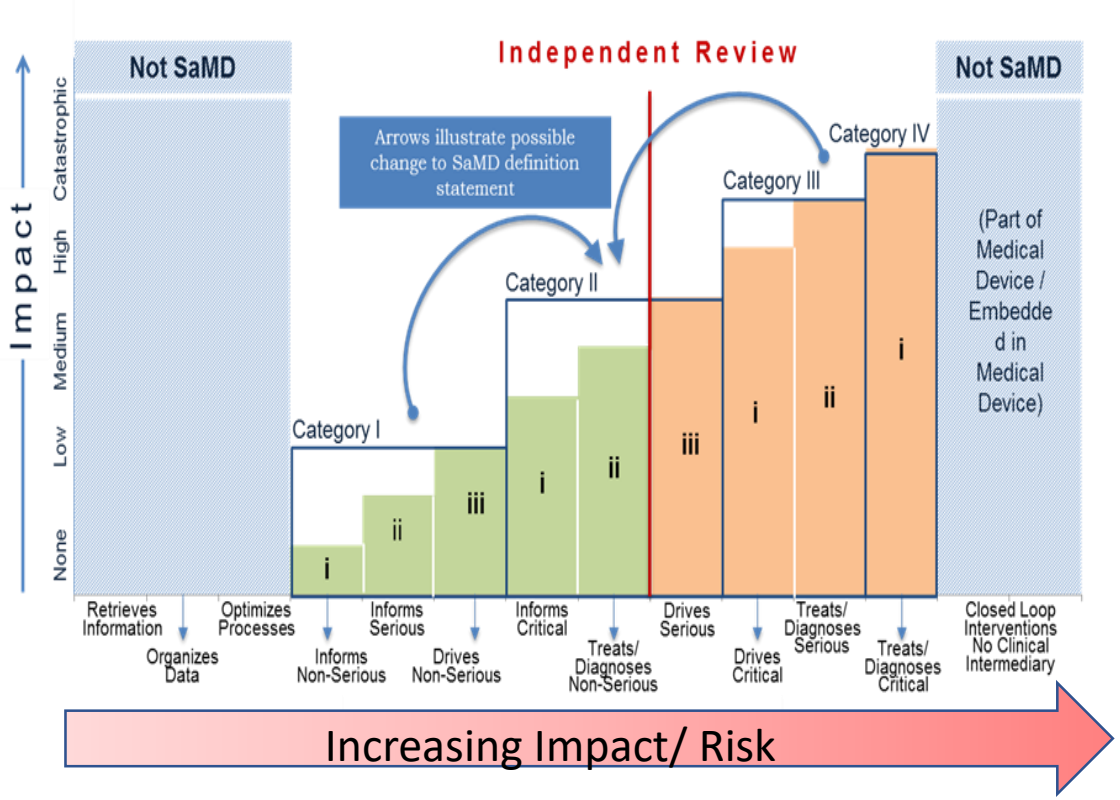
IMDRF International Medical Device Regulators Forum

IMDRF SAMD Risk Categorization

Increasing Significance

Increasing criticality

State of Healthcare Situation or Condition	Significance of Information Provided by SaMD to Healthcare Decision		
	Treat or Diagnose	Drive Clinical Mngmnt	Inform Clinical Mngmnt
Critical	IV	III	II
Serious	III	II	I
Non-Serious	II	I	I



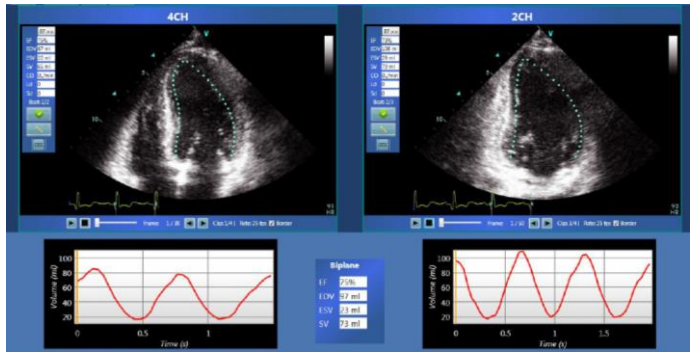
Devices Reviewed in the Division of Radiological Health (DRH)

Overview of Radiological Imaging Devices

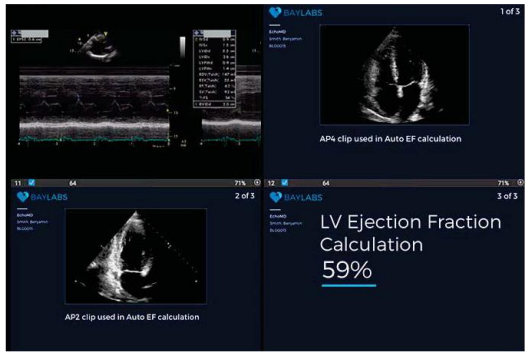
- X-ray, US, CT, MR, PET, Mammography, Radiation therapy including image-guided
- All image acquisition and therapy systems in DRH use software
- DRH regulates many software-only devices that process or analyze images
  - CADe – Computer-aided detection
  - CADx – Computer-aided diagnosis
  - CADx + CADe – Computer-aided detection and diagnosis
  - CADt – Computer-aided triage
  - Image processing software
    - Examples include quantification, image reconstruction, filters, segmentation, artifact reduction, and de-noising
    - Not disease specific, quantitative of anatomical features or function
- Historically, we referred to AI/ML software that analyzes medical images as Computer Aided Detection/Diagnosis/Triage (CADe/CADx/CADt)

Quantitative Imaging – Improved Accuracy and Consistency

- **Example**: K173780 Bay Labs EchoMD
- EchoMD is an AI software device cleared under K173780, using deep learning techniques to automatically evaluate Doppler ultrasound videos of the heart to calculate left ventricular (LV) ejection fraction (EF).
- The predicate device uses simple contrast thresholding techniques for edge detection of the left ventricle to calculate EF.
- Key difference was that the predicate provided an outline of the volume used to calculate LV EF and EchoMD only provided the image used and the numerical value.
- Estimated calculation error was decreased from 20% to 5%.



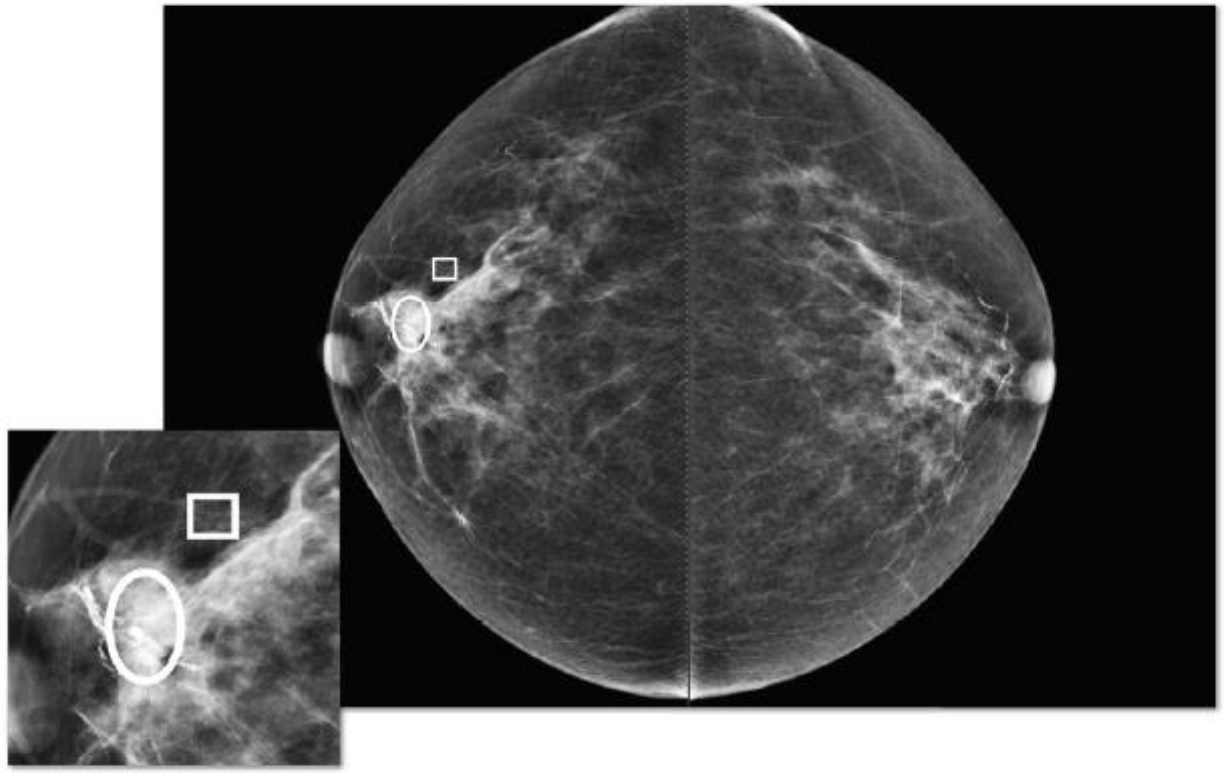
Predicate Device



Subject Device

Computer-Aided Detection (CADe)

- Example: iCAD 2nd Look P010038/ S017
- From approval order … [it] is a computer system intended to identify and mark regions of interest on standard mammomgraphic views to bring them to the attention of a radiologist after the initial reading has been completed…



From www.icadmed.com

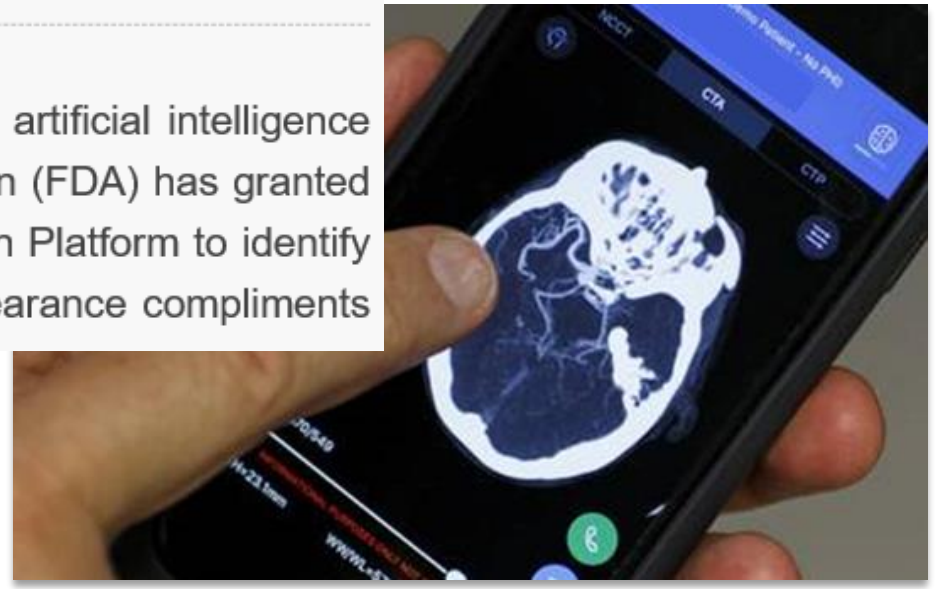
Computer-Aided Triage (CADt) – Prioritization and Triage

- Example: ContaCT DEN170073

Feb 15, 2018 SOURCE: PR NewsWire

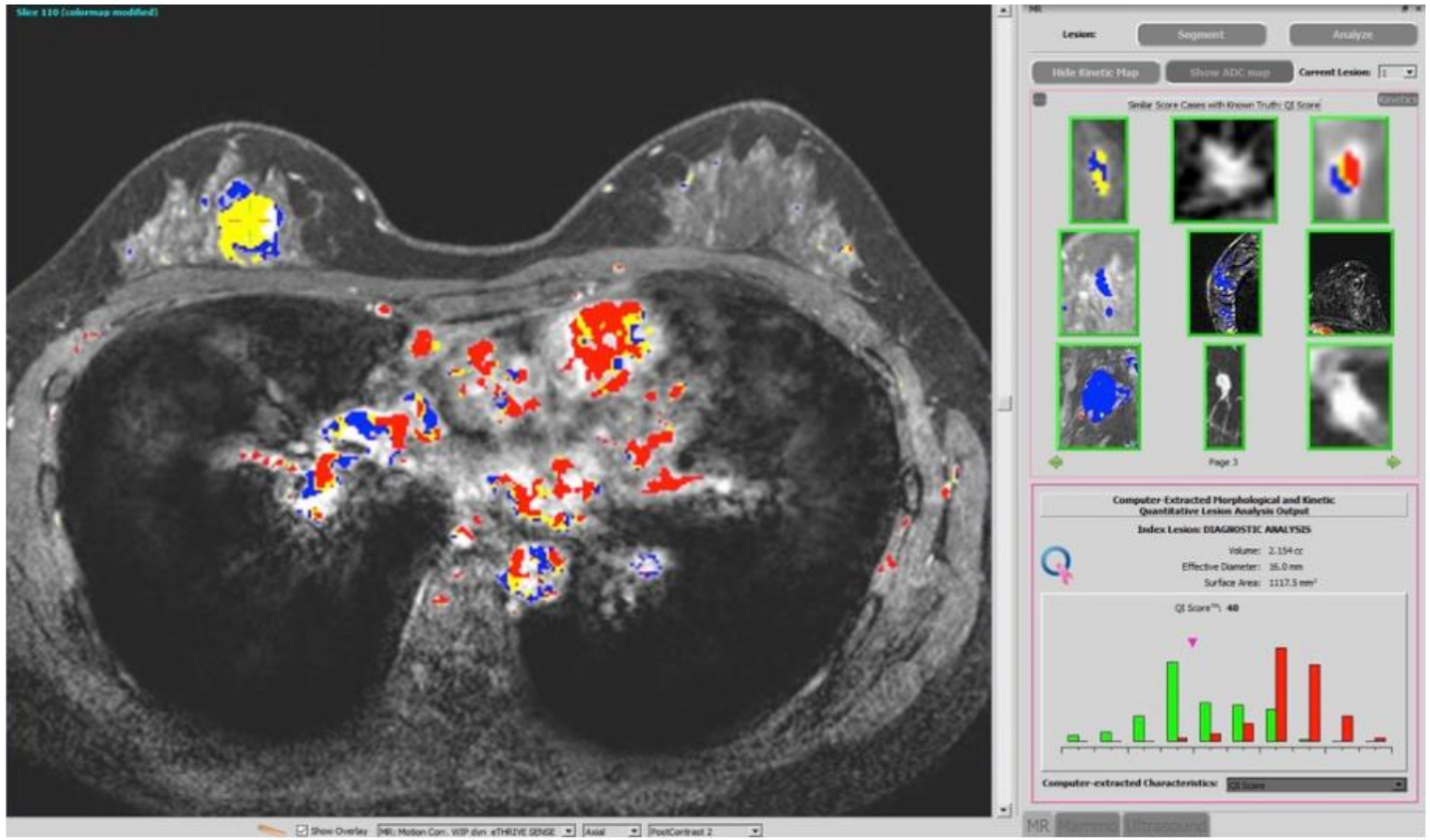
Viz.ai Granted De Novo FDA Clearance for First Artificial Intelligence Triage Software

SAN FRANCISCO, Feb. 15, 2018 /PRNewswire/ -- Viz.ai, Inc., an applied artificial intelligence healthcare company announced that the U.S. Food and Drug Administration (FDA) has granted a De Novo request for the first-ever Computer-Aided Triage and Notification Platform to identify Large Vessel Occlusion (LVO) strokes in CTA imaging. This regulatory clearance compliments



Computer-Aided Diagnosis (CADx)

- Example: QuantX DEN170022



QuantX Advanced includes QI Score™ (bottom right of panel) and Similar Case Compare™ (top right).

Computer-Aided Detection and Diagnosis (CADe + CADx)

- Example: Transpara K181704
- Predicate: DEN180005 – OsteoDetect – Computer Aided Detection and Diagnosis (CADe/CADx) for wrist fracture

Device Name
Transpara™

Indications for Use *(Describe)*

The ScreenPoint Transpara™ system is intended for use as a concurrent reading aid for physicians interpreting screening mammograms, to identify regions suspicious for breast cancer and assess their likelihood of malignancy. Output of the device includes marks placed on suspicious soft tissue lesions and suspicious calcifications; region-based scores, displayed upon the physician's query, indicating the likelihood that cancer is present in specific regions; and an overall score indicating the likelihood that cancer is present on the mammogram. Patient management decisions should not be made solely on the basis of analysis by Transpara™.

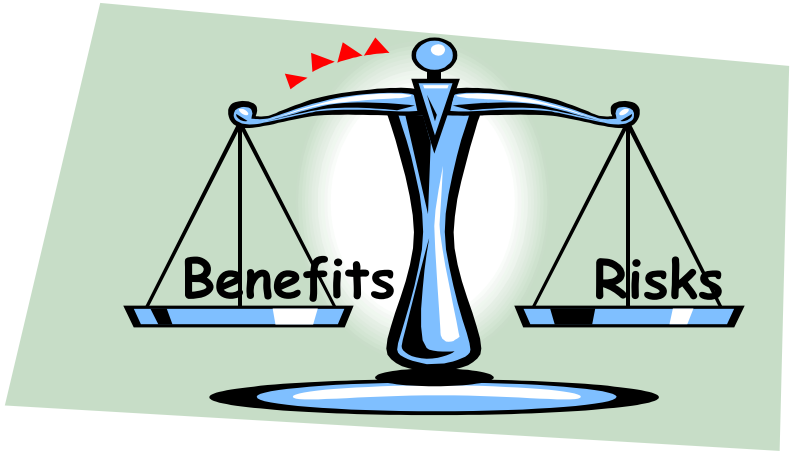
Summary: Recent Clearances and Approvals

- De Novos and 510(k)s:
  - DEN170022 – QuantX – Computer Aided Diagnosis (CADx) for breast cancer
  - DEN170073 – ContaCT – Computer Aided Triage for stroke
  - DEN180005 – OsteoDetect – Computer Aided Detection and Diagnosis (CADe/CADx) for wrist fracture
  - K182373 – PowerLook Tomo Detection V2 – CADe/CADx for breast cancer
- Our regulatory approach will enable many new safe and effective technologies to reach the market without the burden of the PMA process (e.g., CADe)
  - Burdensome and longer timelines
  - Almost always required a full Multi-Reader Multi-Case study
  - Doesn't rely on knowledge gained over past 20 years

Regulatory Review Objectives and Pathways

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



- Total Product Lifecycle (TPLC)
  - Premarket, Compliance, and Post-market Surveillance

Premarket Review of Radiological Imaging Devices

	Class I	Class II		Class III
Risk	Low	Moderate		High
Clearance/Approval	Not required	510(k) Submission	De Novo Classification Request	Premarket Approval (PMA) Application
Comparison	Not required	Predicate Device	Clinical Truth	Clinical Truth
Controls	General	General + Special		Not established
Submission Studies	Not required*	Analytical + Clinical		

↓ ↓ ↓ ↓

Marketed **Cleared** **Granted** **Approved**

*Most Class I and some Class II IVDs are “exempt” from premarket review

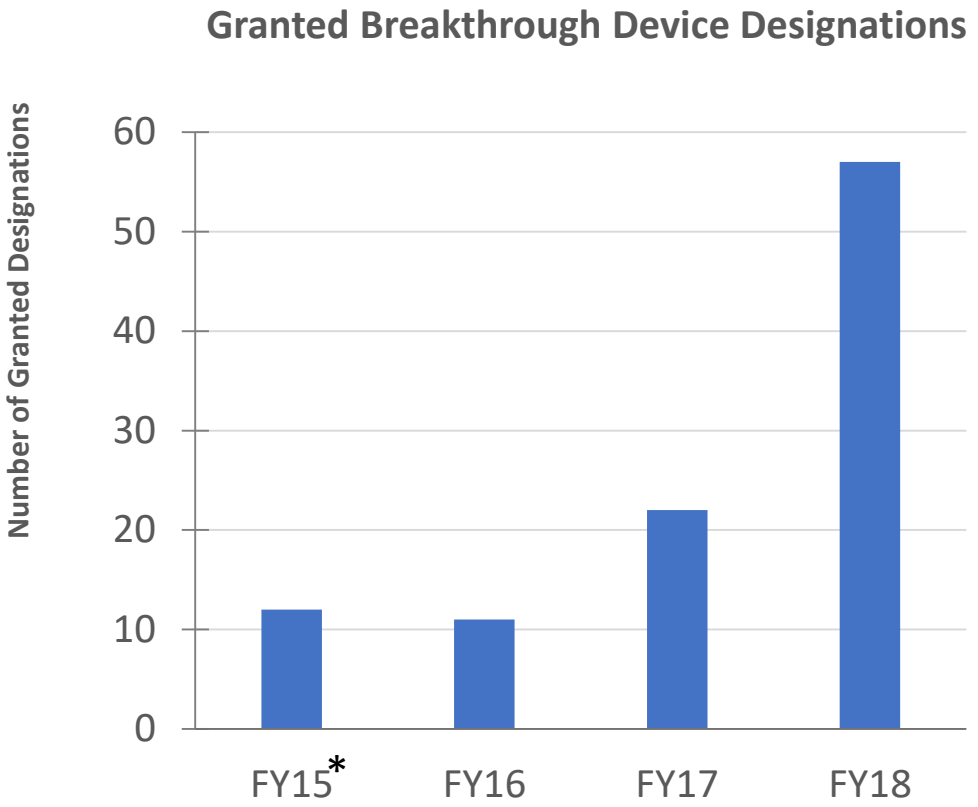
Summary of MDUFA Performance Goals

Submission Type	Action	FDA Review Days
510(k)s	Substantive Interaction	60
	Decision	90
De Novos	Decision	150
Original PMAs & Panel-Track Supplements	Substantive Interaction	90
	Decision if No Panel	180
	Decision With Panel	320
	Decision Following Panel	60
	Response to Approvable	60
180-Day PMA Supplements	Substantive Interaction	90
	Decision	180
Real-Time PMA Supplements	Decision	90
Pre-Submissions	Written Feedback	70 or 5d prior to meeting

Defining time-to-decision goals, including shared goals with industry, aids in getting safe, effective medical devices to healthcare providers and their patients sooner.

Breakthrough Devices

- Help patients have more timely access to devices
- Expedite device development and review for certain medical devices
- Work with sponsors to define a roadmap from early stages of device development to FDA marketing authorization
- Applies to PMA, De Novo, or 510(k) applications and submissions



Breakthrough Devices Program - Guidance for Industry and Food and Drug Administration Staff
www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM581664

Common Submission Components & RTA Process

- Indications for Use (IFU) Statement / Intended Use ***
- Acceptance Checklist (recommended)
- Table of Contents
- Device Description ***
- Truthful and Accurate Statement
- Proposed Labeling ***
- Performance Testing ***

Content of a 510(k) submission: https://www.fda.gov/medical-devices/premarket-notification-510k/content-510k#link_3
Content of a PMA application: https://www.fda.gov/medical-devices/premarket-approval-pma/pma-application-contents
Content of a De Novo classification request: https://www.fda.gov/medical-devices/premarket-submissions/de-novo-classification-request#How_to_Prepare_a_De_Novo_Request

The 510(k) Submission: Demonstrating Substantial Equivalence

- Establish equivalent safety and effectiveness of a proposed device through comparison with a legally marketed predicate(s) – special controls already exist
  - Predicates must not be subject to PMA (e.g., most class III devices)
- Compare indications/intended use and technological characteristics
- 510(k)s can have differences in technology, but they cannot include a new intended use relative to the predicate(s)
  - Differences in technology should not raise different questions of safety or effectiveness
  - Reference devices can help justify the use of certain test methods
  - Benefit-risk is occasionally used to help establish substantial equivalence, covered in next slides

See Appendix A in "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]" issued July 2014: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/510k-program-evaluating-substantial-equivalence-premarket-notifications-510k

Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications (510(k)) with Different Technological Characteristics issued September 2018: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/benefit-risk-factors-consider-when-determining-substantial-equivalence-premarket-notifications-510k

De Novo Classification and PMA Applications: Defining Special Controls & Applying Benefit-Risk Analysis

- Special Controls for Proposed Class II Devices (De Novo only)
- Summary of the Benefits & Risks
  - Benefits: Factors in determining the extent of the probable benefits include the type of benefit, the magnitude of the benefit, the probability of the patient experiencing benefit, and the duration of effect.
  - Risks: FDA considers multiple factors including the severity, types, number, and rates of harmful events associated with the use of the device (including serious adverse events and procedure-related complications); the probability of a harmful event; the duration of harmful events; and, for diagnostic devices, the risk from false-positive or false-negative results.
- Benefit-Risk Analysis: Provide a discussion demonstrating that, when subject to general controls or general and special controls, the probable benefits to health from use of the device outweigh any probable injury or illness from such use.

Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications, issued August 2019 https://www.fda.gov/media/99769/download

Benefit-Risk Assessment

- Summary of B-R Assessment (details are in Appendix B of the guidance)
- Fundamental to decision-making in De Novo and PMA
- Occasionally useful in 510(k)s
  - Decreased benefit + decreased/equivalent risk
  - Equivalent/increased benefit + increased risk

Based on the totality of the data Device Name: PMA/De Novo Number: ☐ Interim ☐ Final	**Proposed Indications for Use**
Assessment of Benefit	Considering benefit in terms of • Type • Magnitude • Probability • Duration of effects • Patient perspective (or care-partner and/or healthcare professional perspectives, if applicable) • Other
1. Is there any evidence of clinical benefit?	☐ YES → Q2 ☐ NO → Do not approve/grant for proposed Indications for Use; proceed to Q9
2. What is the extent of uncertainty for the Benefits?	☐ High ☐ Med ☐Low Continue to Q3
Assessment of Risk	Considering risk in terms of • Severity, types, number and rates of harmful events • Probability of a harmful event • Duration of harmful events • Risks from false-positive or false-negative results • Patient perspective (or care-partner and/or healthcare professional perspectives, if applicable)
3. Are known/probable risks more than minimal?	☐ YES → Q4 ☐ NO → Q4
4. What is the extent of uncertainty for the risks?	☐ High ☐ Med ☐Low Continue to Q5
Assessment of Benefit-Risk	
5. Do the Benefits outweigh the Risks?	☐ YES → Worksheet complete ☐ Unable to conclude that benefits outweigh the risks → Q6
6. Do the Benefits outweigh the Risks, taking into account additional considerations?	☐ YES → Worksheet complete ☐ Unable to conclude that benefits outweigh the risks → Q7
7. Can the risks be mitigated, so that Benefits outweigh the Risks?	☐ YES → Worksheet complete ☐ Unable to conclude that benefits outweigh the risks → Q8
8. Do the Benefits outweigh the Risks considering the use of postmarket actions?	☐ YES → Worksheet complete ☐ Unable to conclude that benefits outweigh the risks → Q9
9. Is there any evidence of clinical benefit for a modified Indications for Use?	☐ YES → Return to Q1 and proceed with modified Indications for Use ☐ NO → Do not approve/grant

Emerging Applications of AI/ML in Radiology & Review Considerations

Graphical data from the quarterly performance reports at:
https://www.fda.gov/industry/medical-device-user-fee-amendments-mdufa/mdufa-quarterly-performance-reports

Looking Toward the Future of AI in Radiology

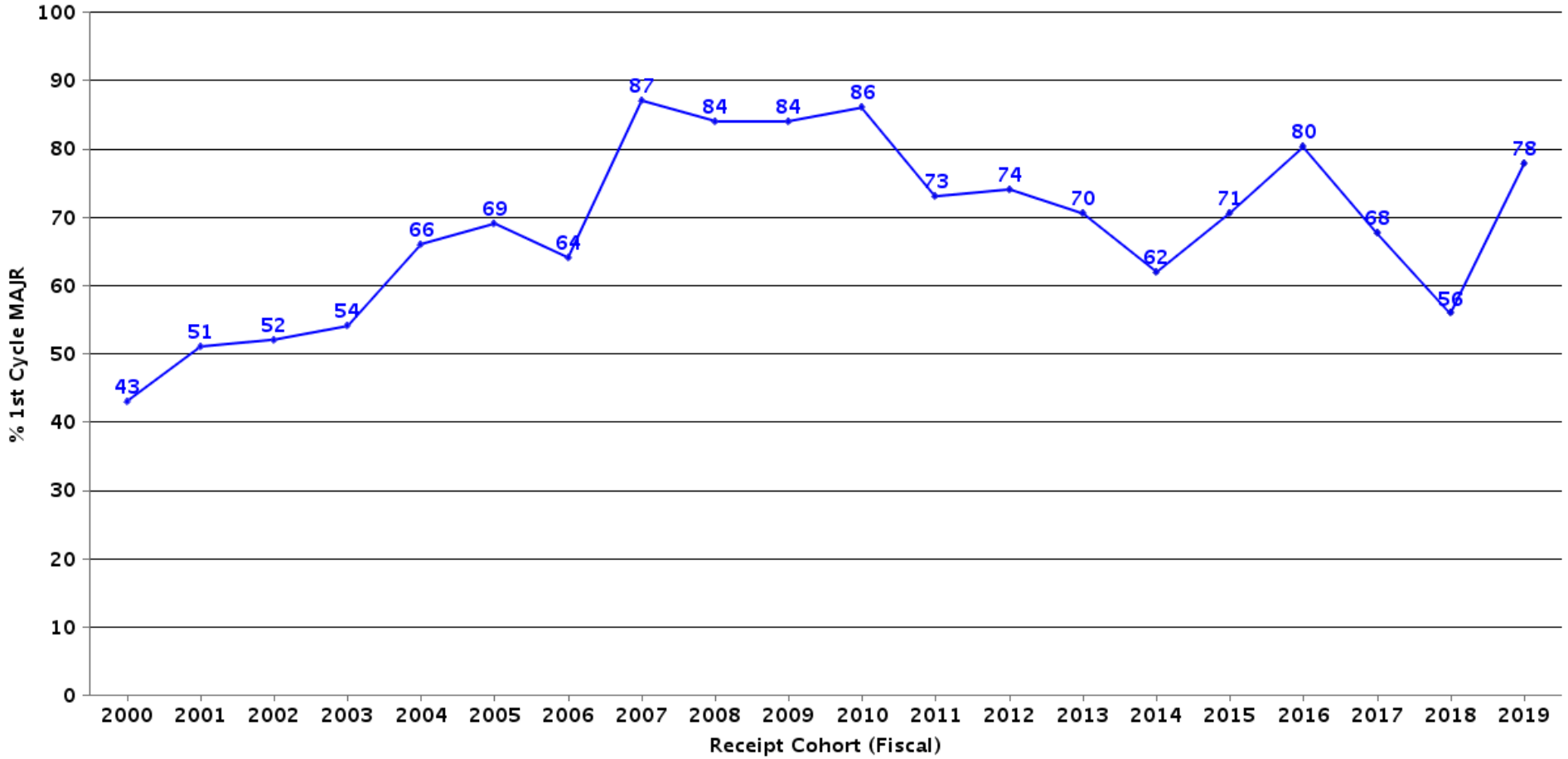
- Changing User's Role in the Radiology Workflow (AI-Assisted Radiology)
  - Ruleout of normals in screening to reduce time spent by radiologists reading through screening exams
  - Automated Detection and diagnosis
  - Treatment recommendations – who gets treated as well as when and how
- Changing Intended User
  - AI-guided image acquisition, for example, could one day allow patients to acquire their own images
  - Allows the use of image acquisition technology in a range of use environments outside the usual professional healthcare environment if an expert sonographer or physician is not always needed to acquire and interpret the images.

Potential Pitfalls in Automation AI Submissions

- Failure to use the Q-submission mechanism to seek feedback from the Agency early regarding benefit-risk, study design, and statistical analysis plan (SAP).
- Ignoring the potential for incidental findings where a physician's historical knowledge, experience, and training cannot be replaced
- Too much too soon. Application scope is too large and frequently aims to rule out or diagnose too many disease states.
- Engineers and scientists developing algorithms frequently have limited experience with clinical study design. The result is a mismatch between study workflow and IFU, and frequently there are no pre-specified endpoints.
- Data double-dipping usage problems or test dataset isolation problems

- The consequence? Deficiencies…

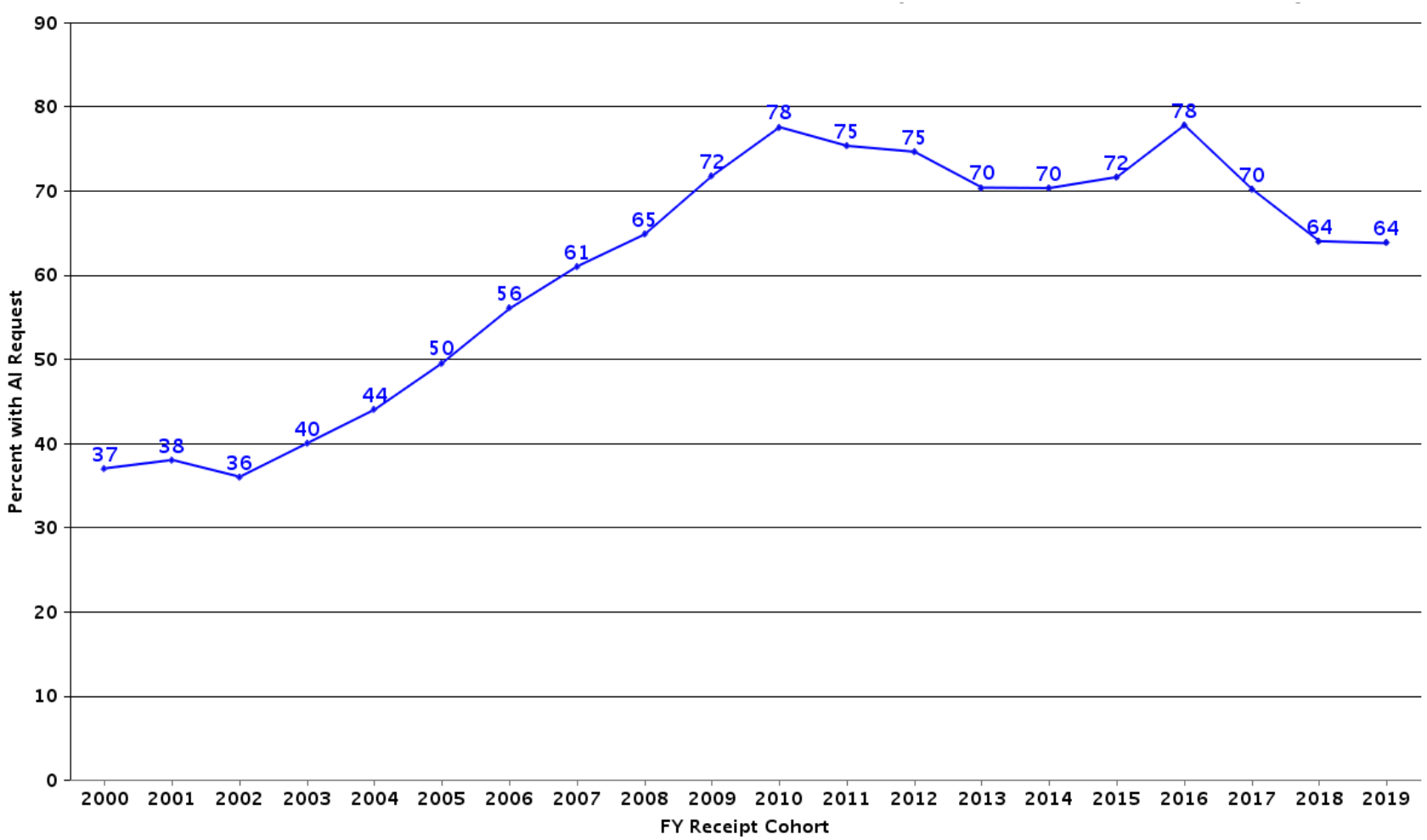
PMA Major Deficiency Rate: Original and Panel Track



Data are based upon the number of submissions that received a major deficiency letter on the 1st review cycle, calculated as a percentage of the number of submissions with a completed 1st review cycle, for submissions rec'd, accepted & filed as of 3/31/19. Note: For the current FY, a Proceed Interactively decision is considered a completed 1st cycle.

◆ % 1st Cycle MAJR PMAO/PTS

% 510(k)s with AI Request in 1st FDA Review Cycle



Keys to a Successful AI Premarket Submission

- Avoid the Common Pitfalls presented previously

- Use the Q-submission mechanism to obtain feedback from the Agency early in the product development lifecycle
  - Remember: Review timeframe for presubmissions is up to 75 days!
  - Craft your specific questions carefully in order to avoid the need for many supplements
  - Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program: Guidance for Industry and Food and Drug Administration Staff
    - www.fda.gov/regulatoryinformation/search-fda-guidancedocuments/requests-feedback-andmeetings-medical-devicesubmissions-q-submission-program

Keys to a Successful AI Premarket Submission

- Do your homework: Only request clearance/approval for intended uses and technology you can successfully test
  - Understand clinical guidelines and practices
  - Understand the special controls (e.g., 510(k)s)
  - Research similar devices in our databases where possible

- Consider different testing methods that are available to streamline the submission and review process. Request feedback regarding your study design in Q-subs.
  - Standalone testing
  - Real world data and registries
  - Streamlined MRMC study designs

- Use a strategic, incremental approach to introduce new technology
  - Example: R2 Image Checker

Looking Ahead

- CDRH would like to hold public meetings to obtain feedback on AI uses that would replace and/or change the user for radiological devices as this would represent a significant change in the practice of medicine.
  - Public workshop is anticipated for the first quarter of 2020
- We continue to encourage proposals/submissions for adaptive learning AI software devices and their postmarket surveillance plans to ensure safe and effective use of these devices.
  - We recommend use of the presubmission Q-sub before submitting a premarket application
- We are working with professional organizations such as the ACR to create tools to streamline the review process by:
  - Providing universal test sets to compare against
  - Expand the use of artificial or synthetic data
  - Ensuring that future adaptive learning programs are improving with time and not getting worse

For More Information…

- CDRH Learn & Divison of Industry and Consumer Education (DICE): https://www.fda.gov/training-and-continuing-education/cdrh-learn
- Q-Submission Program: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program
- Digital Health: https://www.fda.gov/medical-devices/digital-health

Additional Resources

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 (outside of DRH)

Acknowledgments

- Many thanks to my colleagues in DRH and DIDSR for helpful discussions and contributions to this presentation.

Thank you!

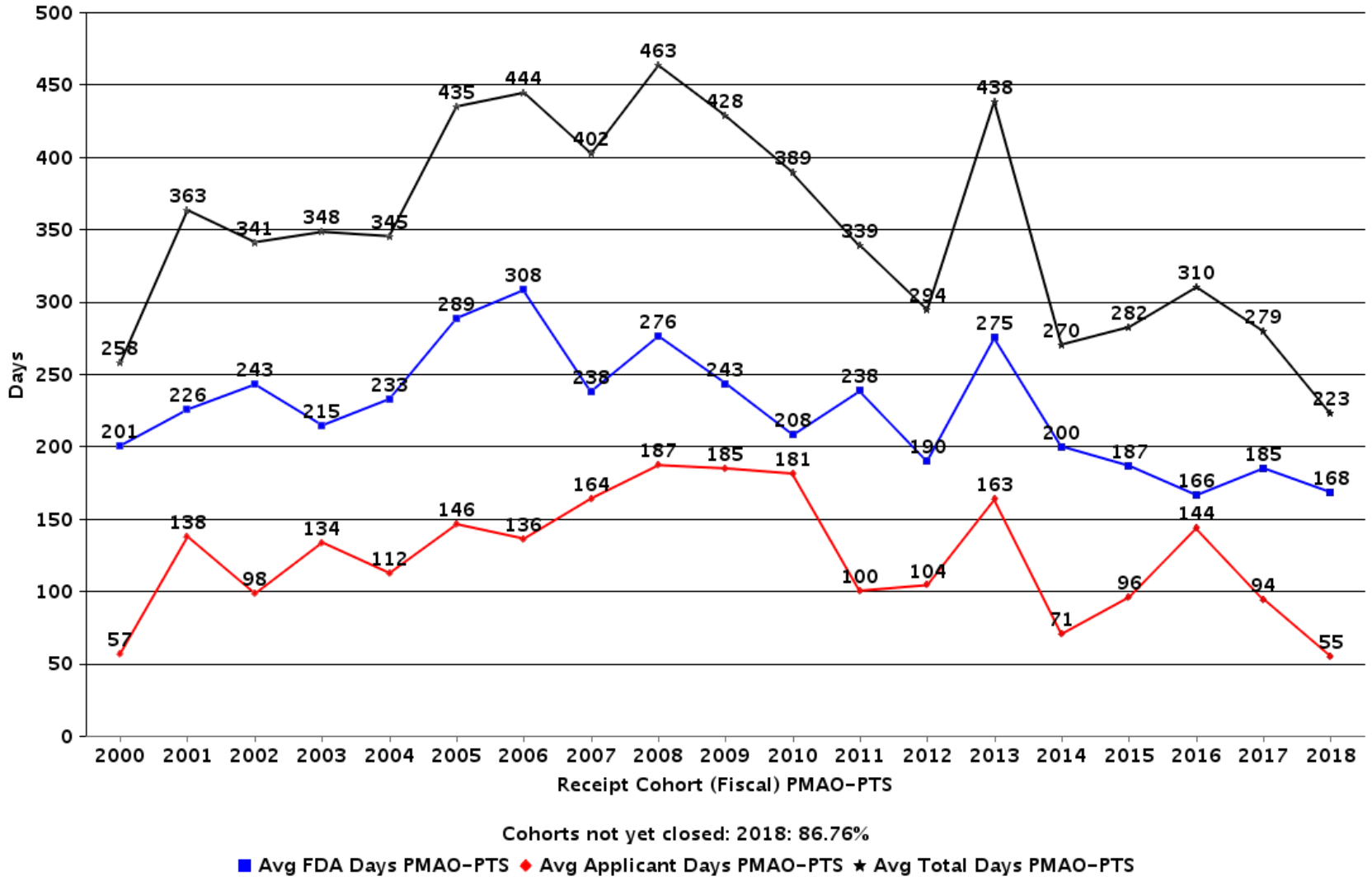
We'll take questions after Brandon's talk…

Data from MDUFA Quarterly Reports

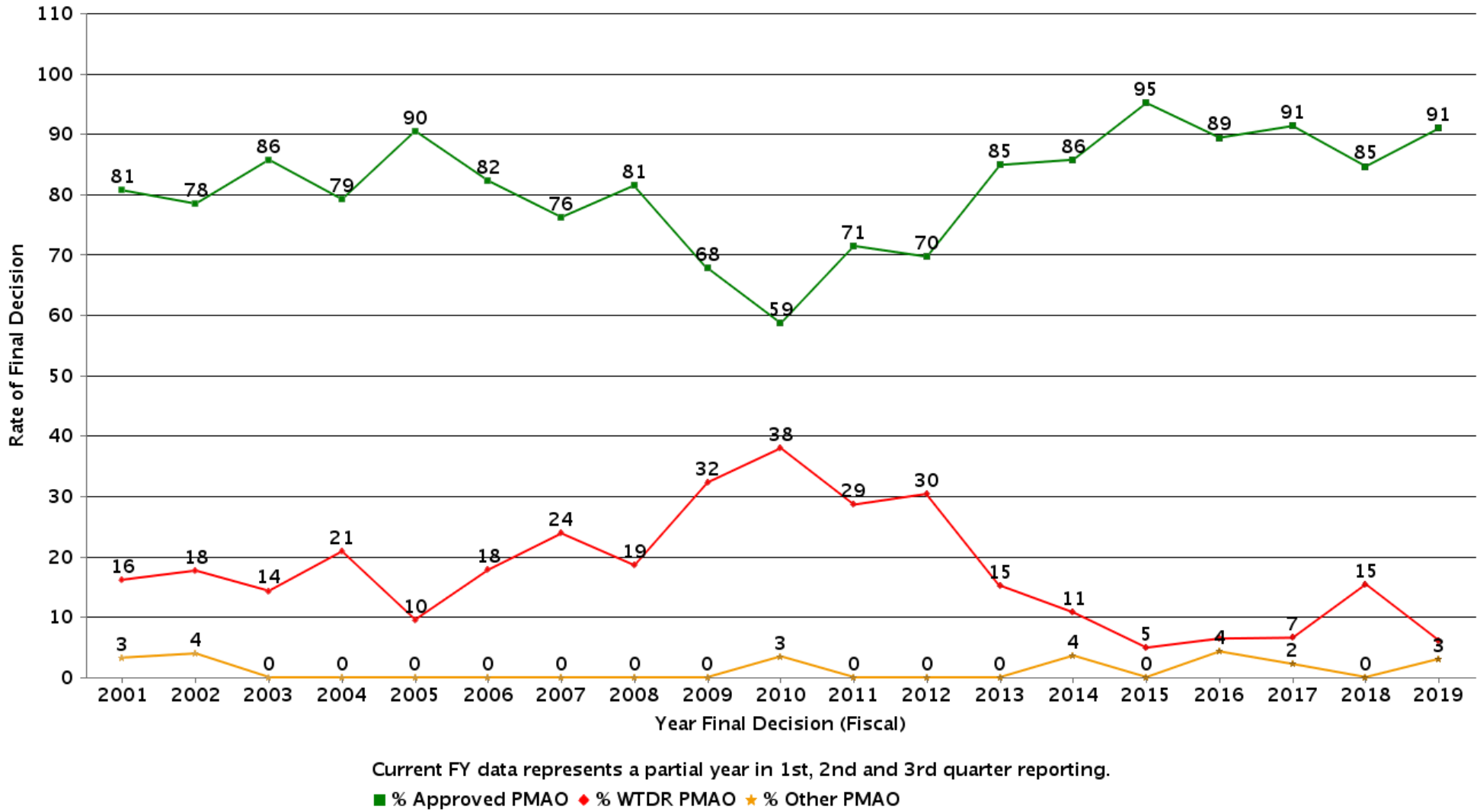
Graphical data from the quarterly performance reports at:
https://www.fda.gov/industry/medical-device-user-fee-amendments-mdufa/mdufa-quarterly-performance-reports

*Please note that the average times will increase as more submissions are closed during subsequent quarters.

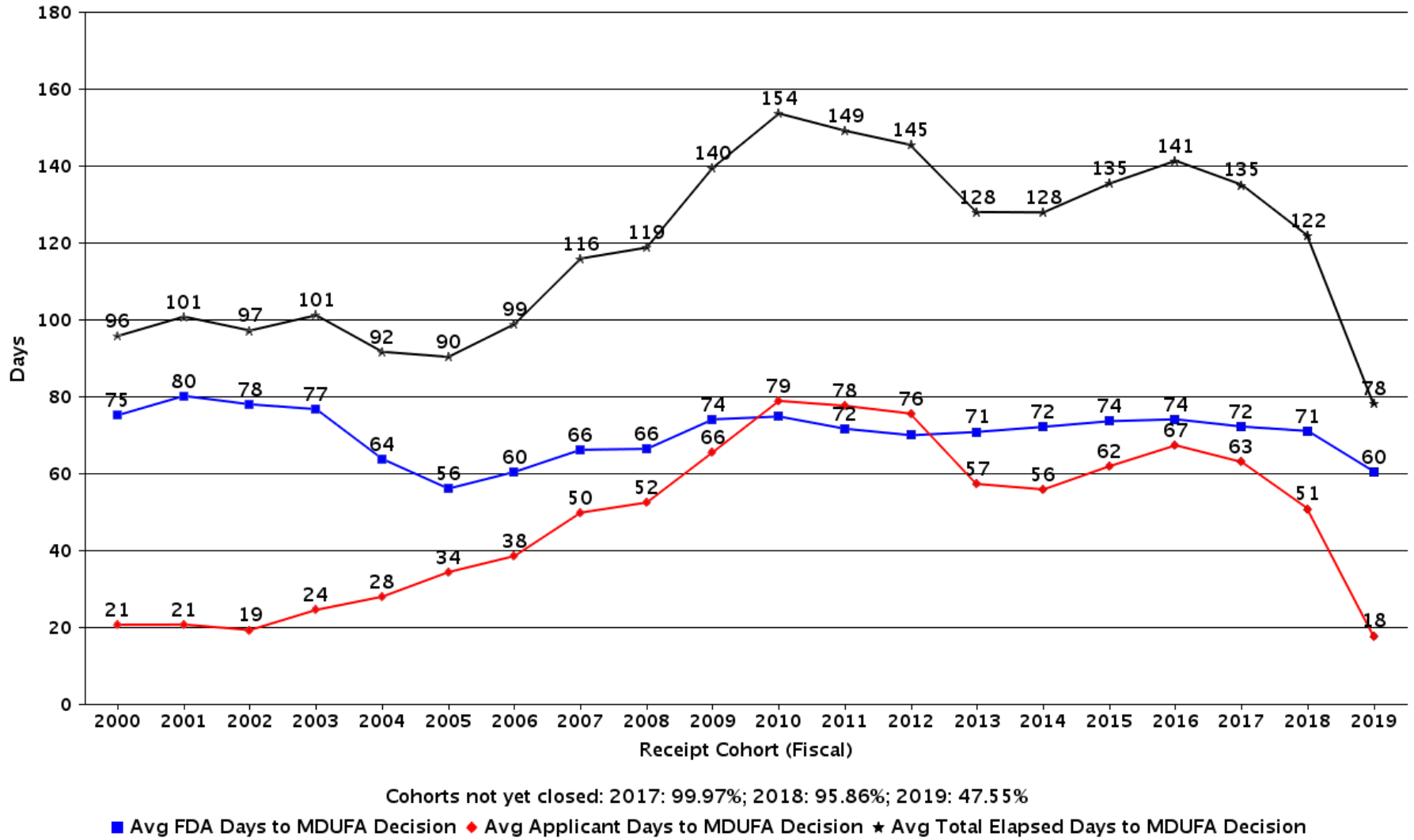
Average Time to MDUFA Decision: Original PMAs and Panel Track



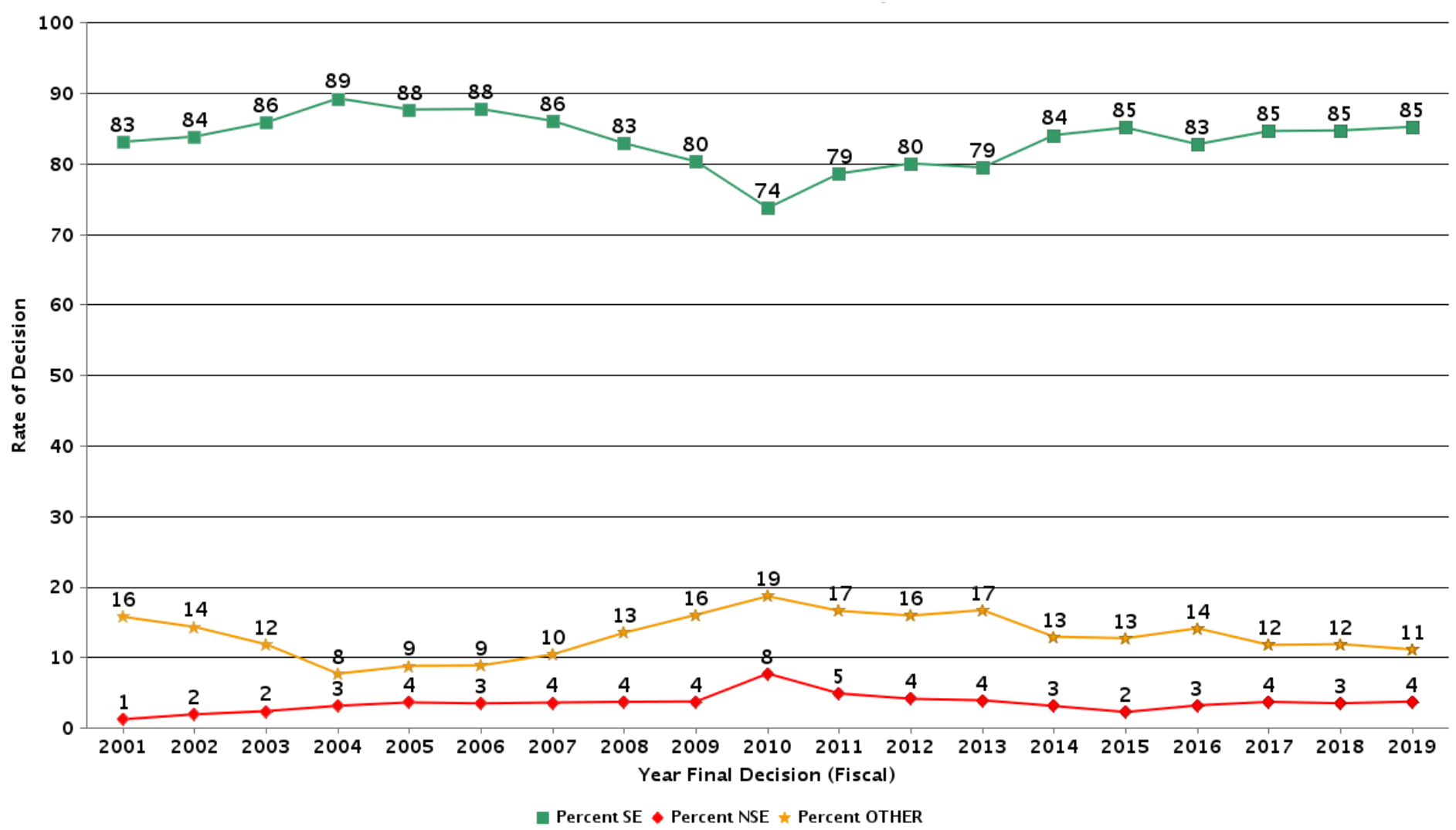
Rates of PMA Approvals, Withdrawals, and Other Decisions



510(k) Average Days to MDUFA (SE/NSE) Decision (6/30/2019)



Rates of SE, NSE, and Other Decisions



Thank you!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