STARTUP ROADSHOW

AI IN HEALTHCARE

Background Information

University of Michigan

Ann Arbor, MI

January 24, 2019

Agenda

- What is artificial intelligence (AI)?
- What are unique consideration of AI?
- How does FDA/CDRH classify a medical device?
- What is FDA/CDRH doing to support advancement of AI?
- What is the Pre-Certification Pilot Program?

What is Artificial Intelligence?

What is Artificial Intelligence (AI) ?

- 2016 U.S. government report, "Preparing for the Future of Artificial Intelligence":

  “Artificial intelligence is a computerized system that exhibits behavior that is commonly thought of as requiring intelligence.”

- Oxford Dictionary:

  "The theory and development of computer systems able to perform tasks that normally require human intelligence, such as visual perception, speech recognition, decision-making, and translation between languages."

- Wikipedia:

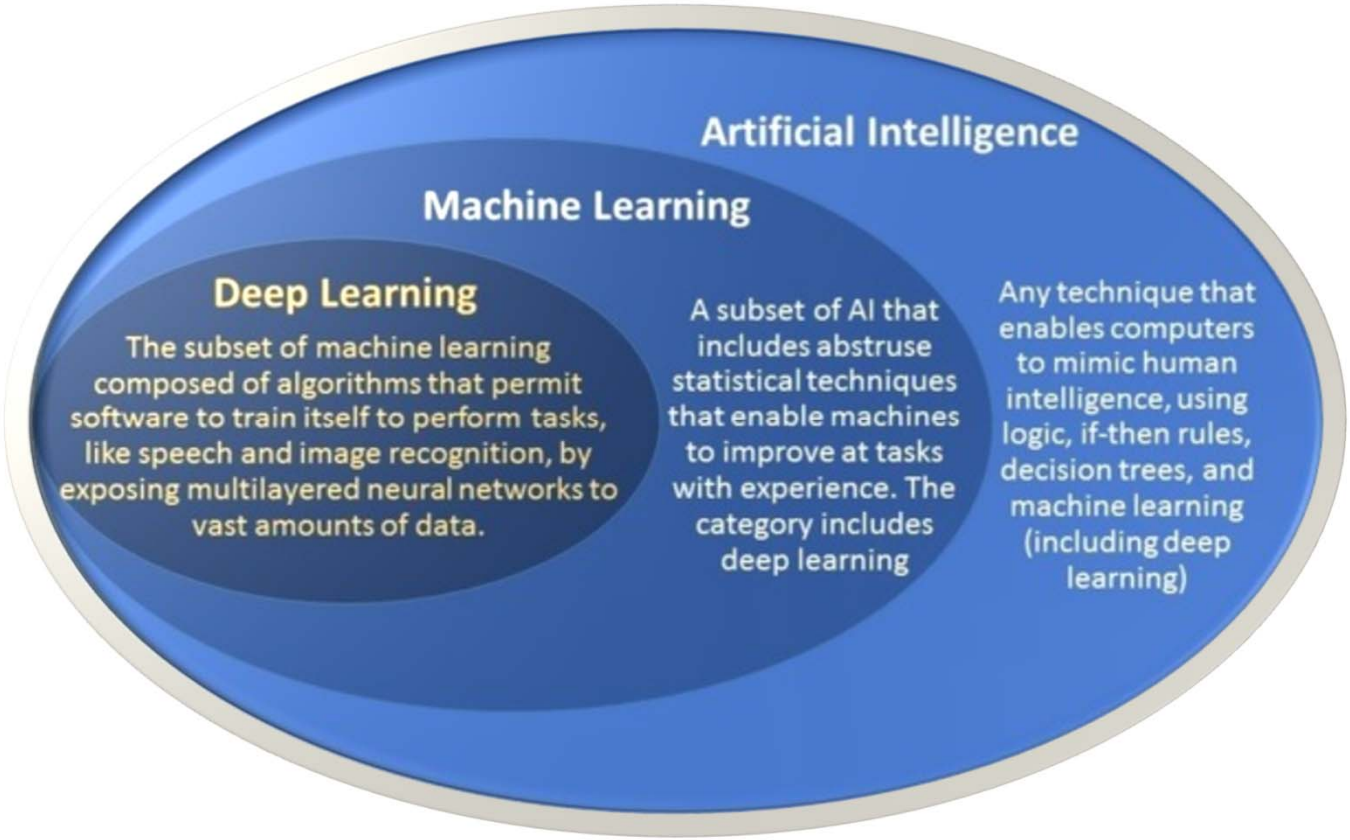
  "In computer science, artificial intelligence (AI), sometimes called machine intelligence, is intelligence demonstrated by machines, in contrast to the natural intelligence displayed by humans and other animals. Computer science defines AI research as the study of 'intelligent agents': any device that perceives its environment and takes actions that maximize its chance of successfully achieving its goals. More in detail, Kaplan and Haenlein define AI as 'a system’s ability to correctly interpret external data, to learn from such data, and to use those learnings to achieve specific goals and tasks through flexible adaptation.' Colloquially, the term 'artificial intelligence' is applied when a machine mimics 'cognitive' functions that humans associate with other human minds, such as 'learning' and 'problem solving'."

What is AI?

Other terms that get mixed with AI include:

- Machine Learning (ML)
- Deep Learning
- Neural Networks
- Knowledge engineering
- Thinking machine
- Natural Language Processing
- ….

What is AI ?



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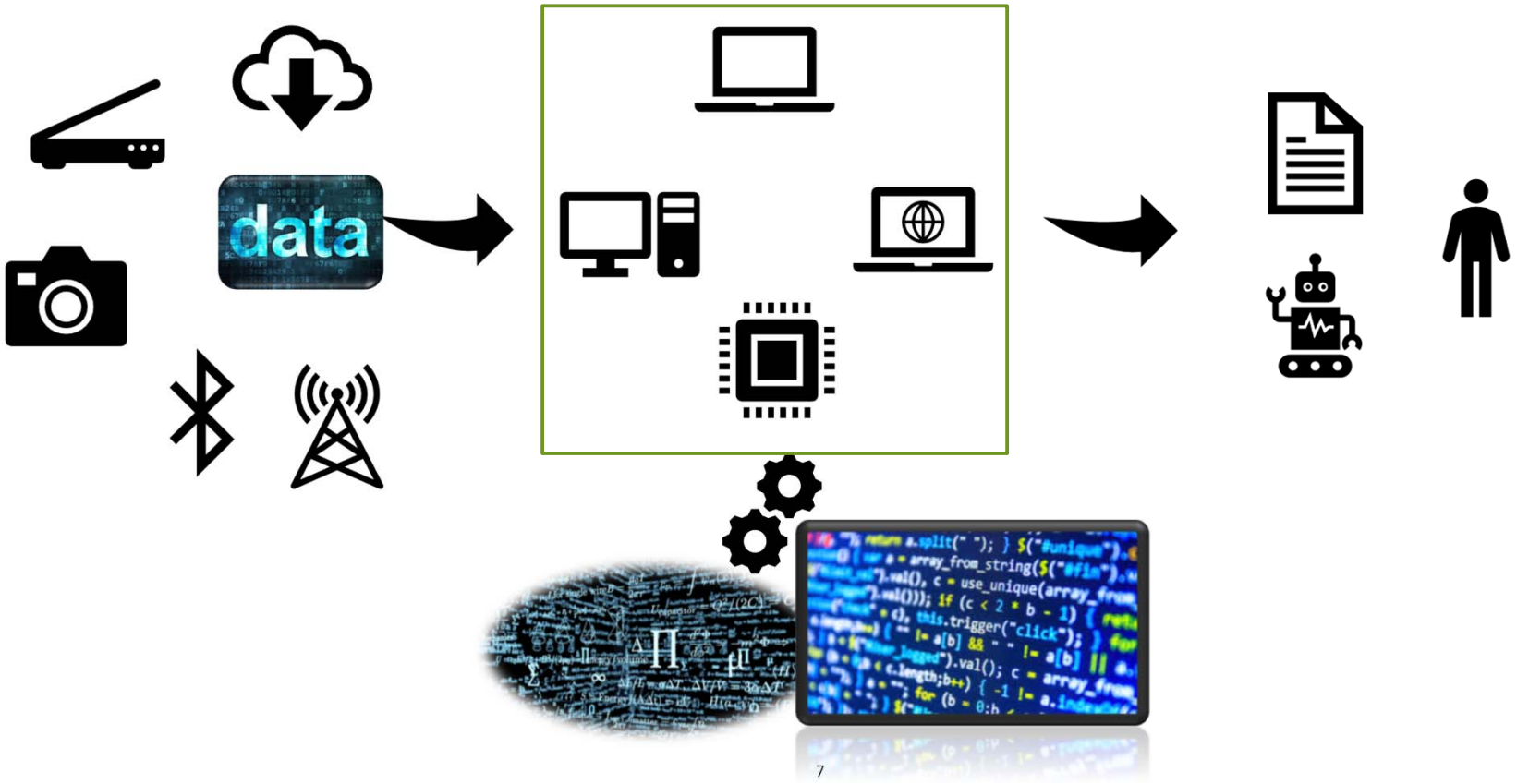
At a basic level, AI is:



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Unique considerations for AI

Unique considerations for AI

- What should it be used for?
- Explainability of the result and algorithm
- How to verify and validate, especially if AI changes based upon data ingested
- Quality / usability of the data (real-world data, different nomenclature, semantics)
- How / when to assess changes in application
- Development speed / processes
- Identifying training and retraining data sets
- Supports intended use
- Mitigating perpetuating bias (distributional shift, sample selection bias)
- How to quantify benefit
- Unable to “err on the side of caution”
- User reliance (automation bias, automation complacency)
- Can optimize to the wrong or unrelated task
- Data could reinforce outmoded practice (may not be able to adjust to radical shifts)

How does FDA regulate medical devices?

WHAT IS A MEDICAL DEVICE?

"(A)n instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

- recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and

which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes. The term "device" does not include software functions excluded pursuant to section 520(o).

Section 201(h) of the Federal Food Drug & Cosmetic (FD&C) Act

WHAT DOES 520(o) SAY?

REGULATION OF MEDICAL AND CERTAIN DECISIONS SUPPORT SOFTWARE.—

(1) The term device, as defined in section 201(h), shall not include a software function that is intended—

(A) for administrative support of a health care facility, including the processing and maintenance of financial records, claims or billing information, appointment schedules, business analytics, information about patient populations, admissions, practice and inventory management, analysis of historical claims data to predict future utilization or cost-effectiveness, determination of health benefit eligibility, population health management, and laboratory workflow;

(B) for maintaining or encouraging a healthy lifestyle and is unrelated to the diagnosis, cure, mitigation, prevention, or treatment of a disease or condition;

(C) to serve as electronic patient records, including patient-provided information, to the extent that such records are intended to transfer, store, convert formats, or display the equivalent of a paper medical chart, so long as—

(i) such records were created, stored, transferred, or reviewed by health care professionals, or by individuals working under supervision of such professionals;

(ii) such records are part of health information technology that is certified under section 3001(c)(5) of the Public Health Service Act; and

(iii) such function is not intended to interpret or analyze patient records, including medical image data, for the purpose of the diagnosis, cure, mitigation, prevention, or treatment of a disease or condition;

(D) for transferring, storing, converting formats, or displaying clinical laboratory test or other device data and results, findings by a health care professional with respect to such data and results, general information about such findings, and general background information about such laboratory test or other device, unless such function is intended to interpret or analyze clinical laboratory test or other device data, results, and findings,

What does 520(o) say?

or

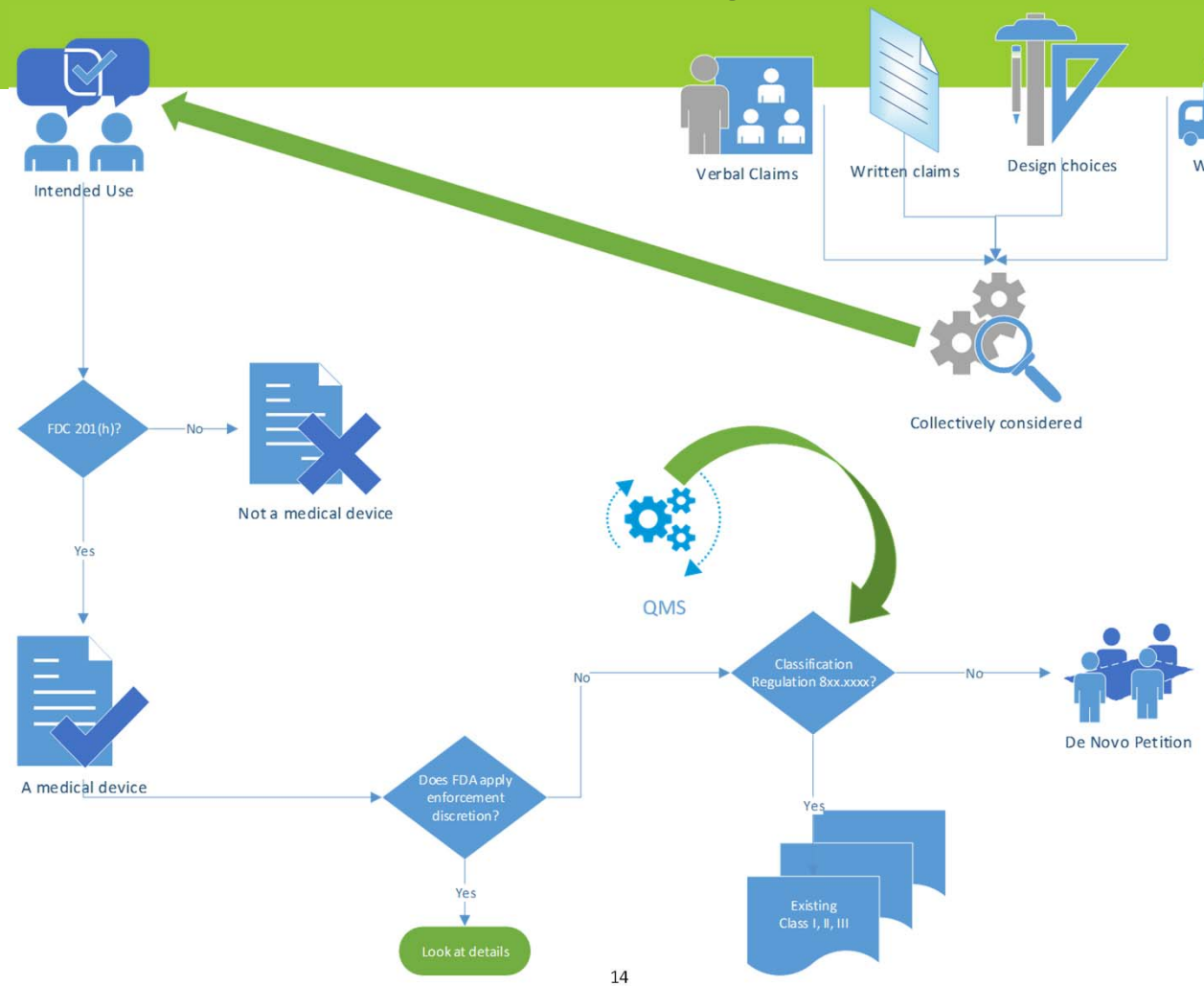
(E) unless the function is intended to acquire, process, or analyze a medical image or a signal from an in vitro diagnostic device or a pattern or signal from a signal acquisition system, for the purpose of—

(i) displaying, analyzing, or printing medical information about a patient or other medical information (such as peer-reviewed clinical studies and clinical practice guidelines);

(ii) supporting or providing recommendations to a health care professional about prevention, diagnosis, or treatment of a disease or condition; and

(iii) enabling 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.

How does FDA determine whether a product is a medical device?



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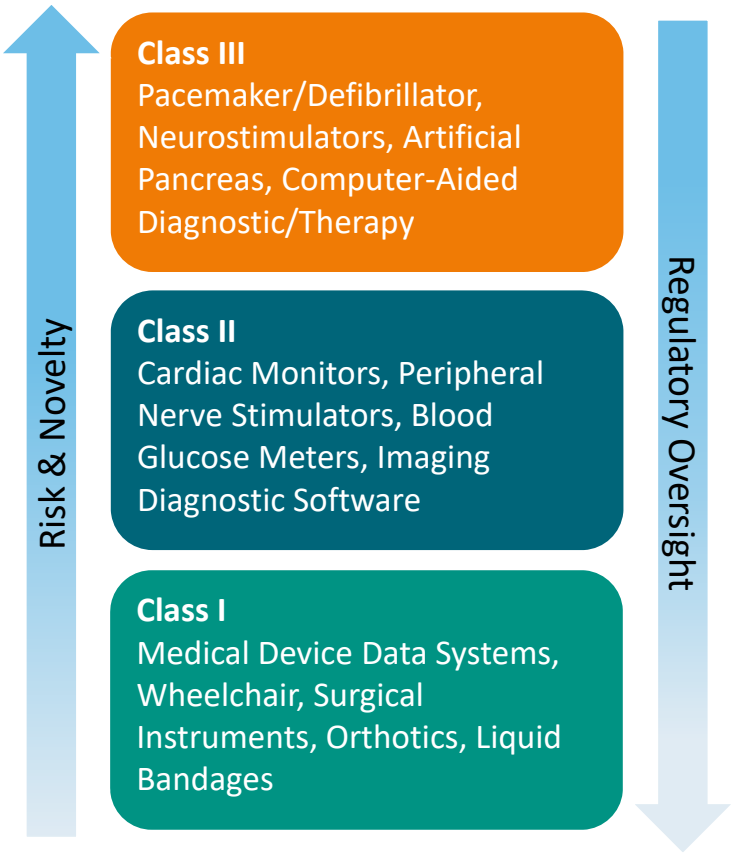
What if it is a medical device?



Regulatory Oversight

- **General Controls**
  - Prohibition against adulterated or misbranded devices
  - Premarket notification 510(k) requirements
  - **Good Manufacturing Practices (GMPs)**
  - Labeling
  - Registration of manufacturing facilities
  - Listing of device types
  - Record keeping
  - Repair, replacement or refund
- Special Controls
- Performance Standards

Regulatory Pathways

- Registration & Listing
- Pre-market Notification
- De Novo Petition
- Pre-market Approval (PMA)

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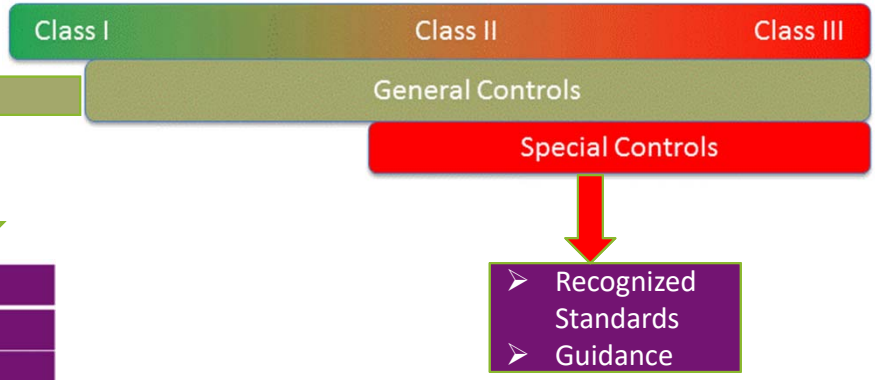
What are general controls?



General Provisions	
Management Responsibility	
Design Control*	
Document Controls	Purchasing Controls
Identification & Traceability	Production & Process Control
Nonconforming Product	Acceptance Activities
Corrective & Preventive Action	Labeling & Packaging Control
Handling, Storage, Distribution & Installation	Records
Servicing	Statistical Techniques

In addition to the general set of medical device regulations, each device type has a specific regulation that describes the device and establishes the device's classification:

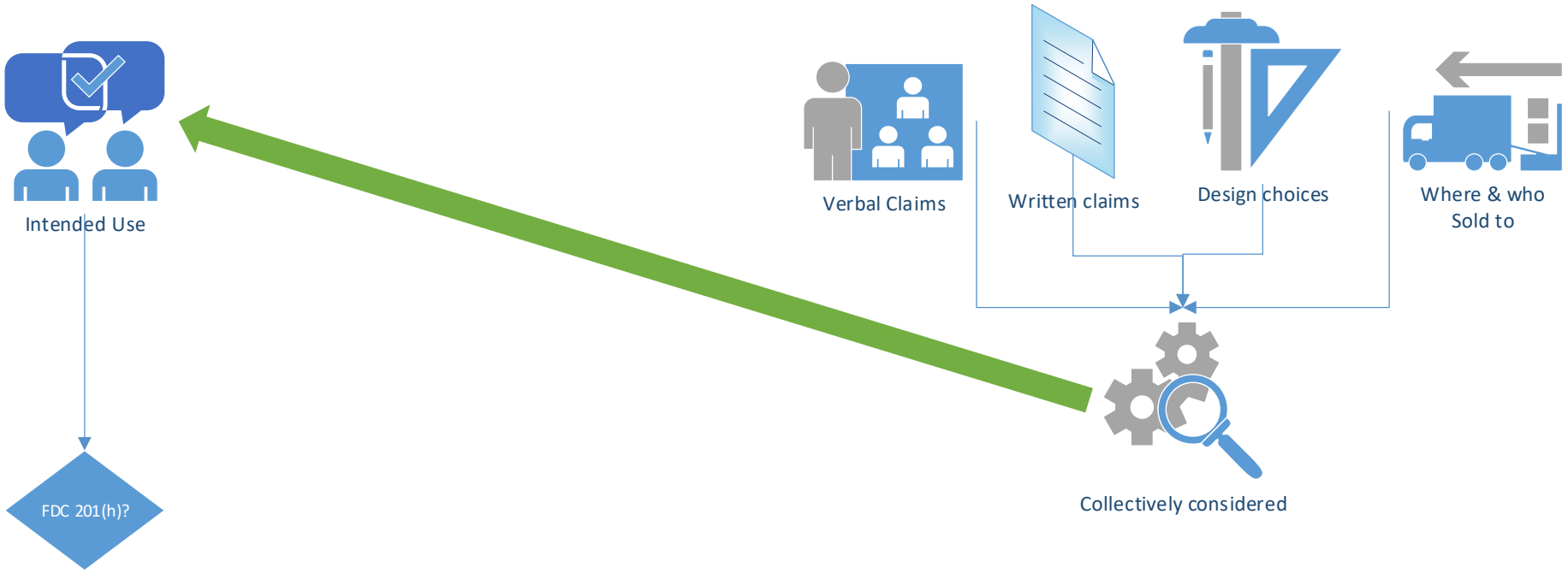
- Example: Infusion Pumps are governed by regulation §21 CFR 880.5725
- Regulation 880.5725 establishes infusion pumps as class II devices

What is a de novo petition?

- Low-risk products that have been classified as Class III because they are no substantially equivalent (SE) to identifiable predicate devices.
- Novel products often do not have a predicate.
  - A predicate is a medical device with the same intended use and technology OR differences in technology do not raise new concerns about safety or effectiveness.
- A company can file the petition to down-classify the product.
- If granted, then a new regulation and set of special controls is established.
- The effort and complexity falls somewhere between a 510(k) and a PMA.

How is FDA regulating devices using AI?

General approach is no different than other devices.



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What is FDA / CDRH doing about AI?

Recent FDA clearance / approvals of AI devices

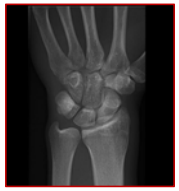
Analyze computed tomography for stroke DEN170073

iz.ai

Analyze images of the eye for diabetic retinopathy DEN180001

IDx

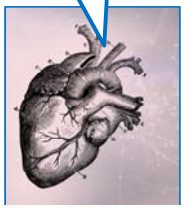
Analyzes cardiology images K163253



Osteodetect

Software analyzes for fracture DEN180005

Automated estimation of left ventricular ejection fraction K173780



BAYLABS

maxQ Artificial Intelligence

Radiological computer aided triage and notification K182177

dreamed DIABETES

Personalized Diabetes Decision Support DEN170043

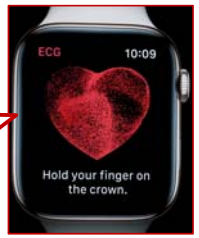
KardiaK Software Platform granted "Breakthrough Device" designation

AliveCor®

zebra MEDICAL.VISION

Evaluates calcified plaques K172983

Electrocardiograph software DEN180044



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FDA activity supporting AI in medical devices

- Breakthrough Devices Program
- 21st Century Cures (§3060, which generated FD&C Act 520(o))
- Guidances
  - Mobile Medical Apps
  - Software as a Medical Device (SAMD): Clinical Evaluation
  - Clinical and Patient Decision Support Software
  - Changes to Existing Medical Software Policies Resulting from Section 3060 of the 21st Century Cures Act
  - Medical Device Data Systems, Medical Image Storage Devices, and Medical Image Communications Devices
  - General Wellness: Policy for Low Risk Devices
  - Design Considerations and Pre-market Submission Recommendations for Interoperable Medical Devices
  - Medical Device Accessories - Describing Accessories and Classification Pathways
  - Cybersecurity
  - Deciding When to Submit a 510(k) for a Software Change to an Existing Device

FDA activity supporting AI in medical devices

- NEST (National Evaluation System for Health Technology)
- Enforcement discretion
- De Novo
- MyStudies app (collection of real-world data)
- Pre-Certification Pilot Program
- Research Activities (Division of Imaging, Diagnostics, and Software Reliability)

What is the Pre-Certification Pilot Program?

FDA's new Software Precertification Pilot Program

Introduction and Overview

- The Software Precertification (Pre-Cert) Pilot Program aims to develop a new regulatory paradigm for SaMD and related digital health technologies that are not believed to be sufficiently addressed via the conventional FDA premarket review process.
- FDA recently issued highly anticipated updates to the Software Pre-Cert Pilot Program for Software as a Medical Device (SaMD). Three documents were issued by FDA.

Pre-Cert Working Model Version 1.0	• Describes major program components and how they interact.
Pre-Cert 2019 Test Plan	• Explains how FDA will confirm assurances of safety and effectiveness for software products evaluated under the program.
Pre-Cert Regulatory Framework	• Describes the Agency's plans to implement the pilot program.

The new Software Precertification Pilot Program

A Working Model: v1.0 – January 2019

The latest Pre-Cert Working Model: What's new?

- FDA's Working Model v1.0 continues the voluntary pathway theme with a goal of maintaining safety and effectiveness of software technologies, without inhibiting patient access to these novel technologies.

Goals of the Pre-Cert Program

- Establish **trust** (that companies have a culture of quality).
- Leverage **transparency** of organizational excellence/product performance.
- Use a tailored **streamlined** premarket review.
- Leverage postmarket opportunities to **verify** continued safety, effectiveness, and performance.

The new Software Precertification Pilot Program

A Working Model: v1.0 – January 2019

Vision of the Pre-Cert Program

- The Pre-Cert Program aims to design a new approach for software products: *a program for the assessment of organizations that perform high-quality software design and testing.*

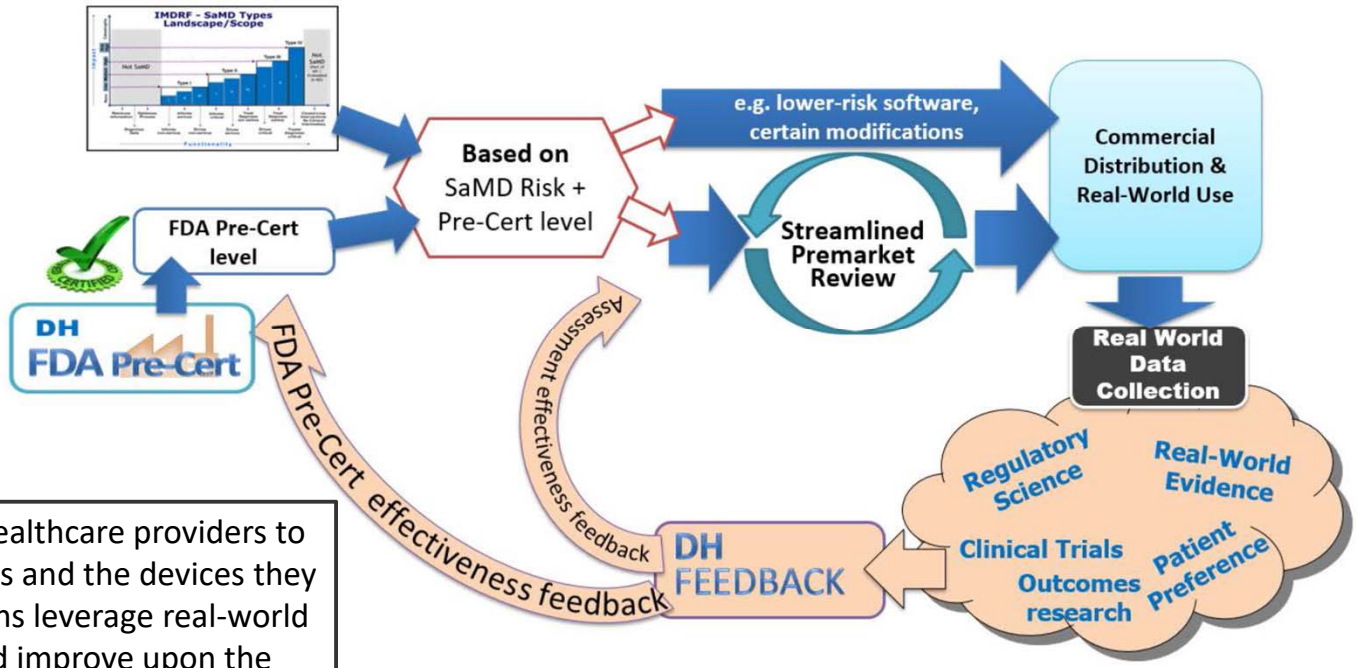
Vison	Under this program, software developers would be assessed (by FDA or by an FDA-accredited third party) for the thoroughness of their quality practices in designing, testing, clinical assessment, and real-world performance monitoring.
	A successful assessment would allow the organization to qualify for a more streamlined premarket review while better leveraging postmarket data collection.
	The software products from precertified **companies must continue to meet the same statutory standards** as software products that have followed the traditional path to market.

The new Software Precertification Pilot Program

A Working Model: v1.0 – January 2019

A reimagined approach for the regulation of software

Vision: to be available for organizations of any size that are currently developing medical devices.



The program should allow patients and healthcare providers to have confidence in precertified companies and the devices they produce because precertified organizations leverage real-world performance to continuously monitor and improve upon the safety and effectiveness of marketed SaMD products.

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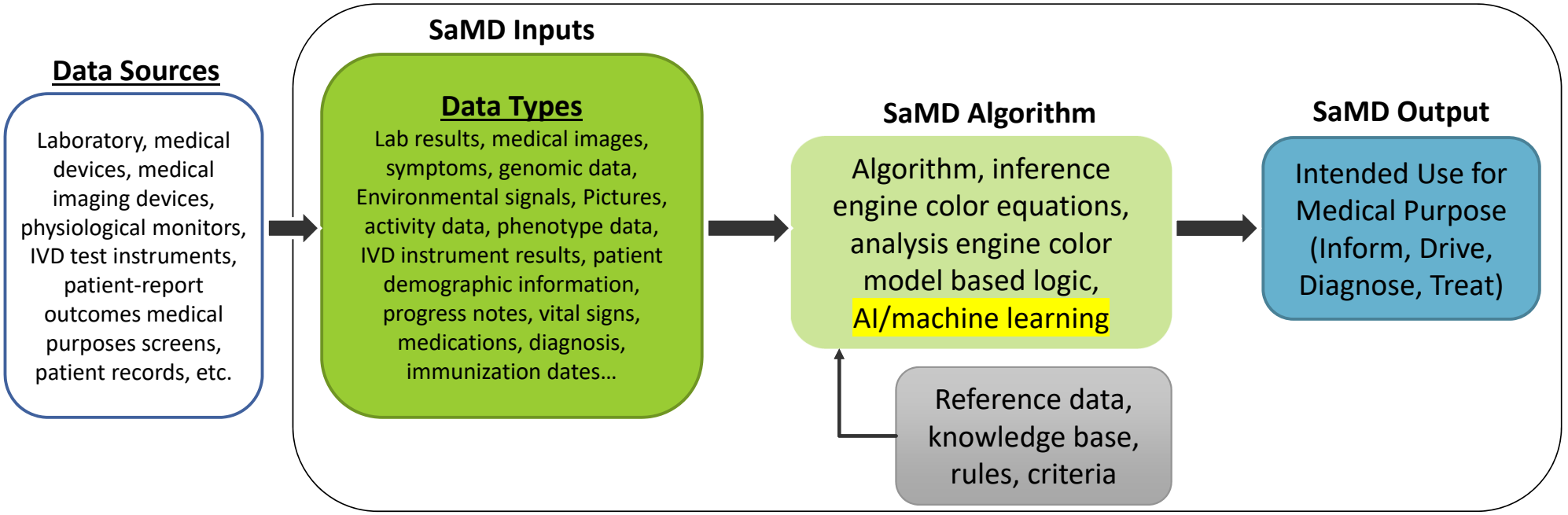
The new Software Precertification Pilot Program

A Working Model: v1.0 – January 2019

The program scope has been limited to SaMD for Version 1.0
(to allow FDA to gain experience in the precertification process)



Description of SaMD, including possible data sources from which inputs are derived and that may be used for one or more medical purposes

The new Software Precertification Pilot Program

A Working Model: v1.0 – January 2019

- **A program to cover the Total Product Lifecycle:**
  - The goal and vision of the Software Pre-Cert Program can be achieved by applying a Total Product Lifecycle approach.
- The program is divided into **four key components:**
  1. Excellence Appraisal
  2. Review Determination
  3. Streamlined Review
  4. Real-World Performance
- Components are interdependent and part of a comprehensive Pre-Cert Program—covering the **"total product lifecycle"** approach.

Software Pre-Cert Program's Four KEY Components

1. Demonstrate a culture of quality and organizational excellence through an **Excellence Appraisal.**

2. Determine the SaMD's required review through **Review Determination**

3. Conduct a **Streamlined Review**

4. Verify a SaMD's continued safety, effectiveness and performance and the organization's commitment to culture of quality through post-market **Real-World Performance**.

The new Software Precertification Pilot Program

A Working Model: v1.0 – January 2019

Software Pre-Cert Program Overview: (1) Excellence Appraisal

FDA would evaluate organizational excellence based on five culture of quality and organizational "Excellence Principles."

Product Quality – Demonstration of excellence in the development, testing, and maintenance.

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.

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The new Software Precertification Pilot Program

A Working Model: v1.0 – January 2019

Software Pre-Cert Program Overview: (1) Excellence Appraisal

- **The main objective of the Excellence Appraisal and precertification component of the pilot program is to develop the process of precertification, identify the elements necessary for the Excellence Appraisal process, and explore best practices for ongoing monitoring of organizational excellence.**

Eligibility

- Any organization that intends to develop/market software that meets the definition of device in section 201(h) of the FD&C Act in the U.S. would be considered in-scope for the Pre-Cert Program.

Appraisal Process

- Not fully developed…but FDA intends to evaluate organizations based on objective/observable evidence. Each organization would determine which processes and **Key Performance Indicators (KPIs)** best meet the elements to comply with requirements.

Excellence Appraisal Scope

- The appraisal is NOT intended to serve as an audit to collect evidence of non-compliance.

Precertification Levels

- **Level 1 Pre-Cert** (allows orgs. to develop/market lower risk software without review while streamlining review for other types of software)
- **Level 2 Pre-Cert** (allows orgs. to develop/market lower and moderate risk software without review while streamlining review for other types of software)

*The FDA does not intend to make organizations' KPI reports available publicly (to the extent consistent with the Freedom of Information Act).

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The new Software Precertification Pilot Program

A Working Model: v1.0 – January 2019

Software Pre-Cert Program Overview: (1) Excellence Appraisal

- FDA will assume responsibility for Software Pre-Cert Excellence Appraisals for 2019, but will consider accreditation of third-party appraisers to conduct reviews in the future.

Third-Party Appraisers	The FDA's vision for the future of the Software Pre-Cert Program includes the identification and accreditation of third parties.
	Third parties would have the capacity and expertise to conduct and Excellence Appraisal.
	Information gathered by third parties would be used as information in FDA's regulatory decision making.

The new Software Precertification Pilot Program

A Working Model: v1.0 – January 2019

Software Pre-Cert Program Overview: (2) SaMD Review Pathway Determination

SaMD Review Pathway Determination

The principal objective: develop a risk-based framework so precertified organizations developing SaMD can determine the premarket review pathway (e.g., flow chart) for their products.

- FDA envisions leveraging the risk category framework for SaMD developed by the International Medical Device Regulators Forum (IMDRF)* to inform the risk category.
- FDA also identified SaMD product-level elements (e.g., the core functionality of the product, device description and performance, intended use, etc.) to be considered to determine SaMD risk categories and Pre-Cert review pathways.

* http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-140918-samd-framework-risk-categorization-141013.pdf

The new Software Precertification Pilot Program

A Working Model: v1.0 – January 2019

Software Pre-Cert Program Overview: (2) SaMD Review Pathway Determination

This table describes a potential future model for a premarket review pathway for SaMD from precertified companies based on:

1. The IMDRF risk category of SaMD
2. Level of precertification of the organization

IMDRF Risk Categorization		Level of Review for Level 1 and Level 2 Precertified Organizations' SaMD		
Type	**Description**	**Initial product**	**Major changes**	**Minor changes**
Type IV	Critical x diagnose/treat	SR	SR	No Review
Type III	Critical x drive		L1 – SR L2 – No Review	
Type III	Serious x diagnose/treat			
Type II	Serious x drive	L1 – SR L2 – No Review	No Review	
Type II	Non-serious x diagnose/treat			
Type II	Critical x inform			
Type I	Non-serious x drive	No Review		
Type I	Serious x inform			
Type I	Non-serious x inform			

Table describes a proposal for when the precertification of organizations and commitment to leverage real-world performance might allow for no premarket review ("No Review" in table above) or streamlined premarket review ("SR" in table above), according to the IMDRF type of the SaMD and the Pre-Cert Level of the organization (Level 1 or Level 2).

The new Software Precertification Pilot Program

A Working Model: v1.0 – January 2019

Software Pre-Cert Program Overview: (3) Streamlined Premarket Review Process

Products that are considered for Streamlined Review are from organizations that have **successfully** gone through the **Excellence Appraisal** (Covered in Step 1: excellence in developing, testing, maintaining, and improving software products).

FDA envisions reviewing the risk management for the device's intended use and the SaMD's clinical evaluation results.

FDA intends to conduct an interactive review supported by automated analysis and then will provide a decision on the marketing of the precertified orgs. SaMD product within a shorter timeframe than traditional premarket review processes.

At a high level, the **Streamlined Review** process would include:

- Understanding the product: FDA would use information from a Review Determination Pre-Sub to facilitate a better understanding of the product
- Premarket review: FDA envisions evaluating the SaMD's analytical performance, clinical performance, and safety measures.
- Marketing authorization: FDA would make a premarket decision.

The new Software Precertification Pilot Program

A Working Model: v1.0 – January 2019

Software Pre-Cert Program Overview: (3) Streamlined Premarket Review

The following elements in the table would be reviewed to provide a reasonable assurance of safety and effectiveness.

Elements necessary for Streamlined Premarket review include examples such as clinical algorithms, cybersecurity-related info (including threat models), software architecture, etc.

NOTE: The FDA expects to implement a process where repeated unsuccessful streamlined reviews of a precertified organization's SaMD trigger a reassessment of the organization's precertification determination.

Streamlined Review Elements
Administrative Elements
Cover letter
Financial Certification and Disclosure Form
Truthful and Accuracy Statement
Product-Specific Elements
Clinical algorithm
Clinical Data Analysis and Interpretation
Cybersecurity product-specific information including threat model
Declaration of Conformity and Summary Reports for Vertical Standards
Hazard Analysis (product-specific)
Instructions for use
Labeling review
Regulatory Pathway Specific Items (e.g., 510(k) substantial equivalence comparison)
Requirements (product-specific)
Revision history
SaMD product demo
Software architecture
Validation (product performance)
Elements Leveraged from other components
Excellence Appraisal Assessment
Review Determination information (Indications for Use, Device Description, etc.)
Real-world Performance Plan

The new Software Precertification Pilot Program

A Working Model: v1.0 – January 2019

Software Pre-Cert Program Overview: (4) Real-World Performance

- During the Excellence Appraisal, all organizations would demonstrate the capability to collect and analyze post-launch **Real-World Performance (RWP)** data. FDA expects that these organizations will consistently collect and analyze readily available post-launch data related to the safety, effectiveness, and performance of their products.

The **real-world performance analytics** component of Version 1.0 of the Software Pre-Cert Program is designed to assess:

Real-World Health Analytics: analyses of real-world clinical outputs and outcomes related to the intended use of the SaMD product.

User Experience Analytics: analyses of user experience outputs related to the real-world use of a SaMD product.

Product Performance Analytics: analyses of outputs and outcomes demonstrating the real-world accuracy, reliability, and security of a SaMD product.

NOTE: FDA intents to focus its post-launch product monitoring efforts on trends and summary analytics, rather than on raw data.

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