DIGITAL HEALTH @ FDA
AN UPDATE...
May 1, 2019

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Effects of Moore’s Law

1. The accelerating pace of change...

Agricultural Revolution: 8,000 years
Industrial Revolution: 120 years
Light-bulb: 90 years
Moon landing: 22 years
World Wide Web: 9 years
Human genome sequenced: 20 years

2. ...and exponential growth in computing power...

Computer technology, shown here climbing dramatically by powers of 10, is now progressing more each hour than it did in its entire first 90 years.

3. ...will lead to the Singularity

Apple II: At a price of $1,298, the compact machine was one of the first massively popular personal computers.

Image Credit: Time Magazine
Digital tools can provide consumers with valuable health information.

Consumers who are better informed about health make better decisions.

What qualifies as a digital health product?

What digital health technologies need regulation?
Digital Health Technology

Digital health technology is the convergence of computing power, connectivity, sensors, and software used in healthcare.

- Used as a medical product;
- Incorporated into a medical product (include a pharmacologic product);
- Used to develop a medical product;
- Used to study a medical product;
- Used as a companion or adjunct to a medical product, including diagnostics and therapeutics.
Goals for a Tailored Regulatory Framework

**Fostering Responsible Digital Health Innovation**

- Enhance patients access to high quality digital medical products
- Enable manufacturers to rapidly improve software products with minor changes
- Maintain a reasonable assurance of safety and effectiveness
- Minimally burdensome

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The Need for a Tailored Approach

*While maintaining reasonable assurance of safety and effectiveness*

**Today’s Device World**  
(Hardware-based)

- **Product Development Timeline**
  - Months to years +
  - Less frequent modifications

- **Postmarket Data**
  - Limited availability and access to real world data (522, PAS, MDRs, MedSun)

- **FDA Premarket Program Volume:**
  - Stable (~3,500 510(k) submissions / 2200 pre-submissions)

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**Digital Health Device World**  
(Software-Based)

- **Product Development Timeline**
  - Weeks to months *(incremental, iterative)* +
  - Frequent modifications

- **Postmarket Data**
  - Potential for **high availability** and access to rich real world data (benefits and risks)

- **FDA Premarket Program Volume:**
  - Potential for **exponential** increase in volume of submissions
FDA Pre-Cert Program

An organization-based streamlined regulatory approach for

Software as a Medical Device (SaMD) that relies on a demonstrated

Culture of Quality and Organizational Excellence
Concept: A Reimagined Approach Using FDA Pre-Cert

Based on SaMD Risk + Pre-Cert level

Streamlined Premarket Review

e.g. lower-risk software, certain modifications

Commercial Distribution & Real-World Use

Real World Data Collection

DH FEEDBACK

Regulatory Science

Real-World Evidence

Clinical Trials Outcomes research

Patient Preference

FDA Pre-Cert level

DH

FDA Pre-Cert

FDA Pre-Cert effectiveness feedback

Assessment effectiveness feedback
Five Excellence Principles Proposed

- **Patient Safety**: Demonstration of a commitment to providing a **safe patient experience**, and to emphasizing patient safety as a critical factor in all decision-making processes.

- **Product Quality**: Demonstration of a commitment to the development, testing, and maintenance necessary to deliver SaMD products at the **highest level of quality**.

- **Clinical Responsibility**: Demonstration of a commitment to responsibly **conduct clinical evaluation and to ensure that patient-centric issues** including labeling and human factors are appropriately addressed.

- **Cybersecurity Responsibility**: Demonstration of a **commitment to protect cybersecurity**, and to proactively address cybersecurity issues through active engagement with stakeholders and peers.

- **Proactive Culture**: Demonstration of a commitment to a **proactive approach** to surveillance, assessment of user needs, and continuous learning.
Reimagining the Regulatory Approach

While maintaining reasonable assurance of safety and effectiveness

**CURRENT PATHWAY**

**Today’s Device World (Hardware-based)**
- Pre-Market Organization-Level Data
- Pre-Market Product-Level Data
- Post-Market Data

**PRE-CERT PATHWAY**

**Digital Health Device World (Software-Based)**
- Leverages real world performance data
- Shortens the timeline for premarket product review
- Adds appraisal of company’s culture of excellence

While maintaining reasonable assurance of safety and effectiveness
FDA’s Software Precertification Pilot Program

- **Building** a working model with continuous public input.
- **Working** with nine participating companies (large and small).
- **Testing** v1.0 throughout 2019 to ensure the same level of safety and effectiveness of products as compared to our traditional approach.
Our Goals For a New Model

How can a pre-certification program address the evolving needs of SaMD products?

Enable a tailored, pragmatic, and least burdensome regulatory oversight that

1. **Assesses** organizations to establish trust that they have a culture of quality and organizational excellence such that they can develop high quality SaMD products;

2. Leverages **transparency** of organizational excellence and product performance across the entire lifecycle of SaMD;

3. Uses a tailored **streamlined** premarket review;

4. Leverages unique postmarket opportunities available in software to **verify** the continued safety, effectiveness, and performance of SaMD in the real world.
Pre-Cert Update: Working Model v1.0

The Software Precertification Working Model v1.0 published on Jan 7, 2019 and included the following changes:

1. A description of the **Total Product Lifecycle approach**
2. Revisions to **Excellence Appraisal** (EA) descriptions for levels of Pre-Cert and FDA’s intention to conduct appraisals in 2019;
3. Revisions to SaMD product-level elements for **review determination**;
4. A proposed list and descriptions of review elements for **streamlined review**, and an updated review process to apply to all submission types;
5. An updated description of the process for developing a **Real World Performance** analysis plan, examples of analytic types/sources, and how the types of RWP collected & the duration of collection may vary.
Regulatory Framework

FDA intends to implement Pre-Cert Pilot Program under the De Novo Pathway so that Excellence Appraised sponsors may:

1. **Submit a “Pre-Cert De Novo”** to receive device classifications through De Novo Pathway by submitting all applicable required information to FDA at different times (i.e., during the Excellence Appraisal, Review Determination, and Streamlined Review);

2. **Submit a Review Determination pre-sub** to confirm a SaMD sponsor is excellence appraised and is eligible for 510(k) under device classification created by Pre-Cert De Novo;

3. **Submit “Pre-Cert 510(k)”** under device classification created by Pre-Cert De Novo containing product-level information on modifications while leveraging EA data to satisfy some required elements of a 510(k) submission.
2019 Test Plan

FDA intends to perform testing of the Pre-Cert program model before establishing it as an alternative premarket pathway for SaMD:

The Test Plan will assess whether Excellence Appraisal (EA) and Streamlined Review (SR) components together produce an equivalent basis for a determining reasonable assurance of safety and effectiveness, as compared to the traditional paradigm.

1. Retrospective Testing: Internally FDA is conducting retrospective tests of SaMD submissions that FDA previously reviewed.

2. Prospective Testing: FDA is working with Pilot Participants who volunteer submissions to apply both the proposed Pre-Cert pathway and the traditional review process;

3. Evaluation of Findings: Demonstrate that the evidence collected through EA and SR processes align to satisfy regulatory requirements for safety and effectiveness.
Determining Equivalency

The Test Plan will assess whether Excellence Appraisal and Streamlined Review components together produce an **equivalent basis** for determining a reasonable assurance of safety and effectiveness, as compared to the traditional paradigm.

**Today’s Device World** (Hardware-based)

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- Pre-Market Product-Level Data
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**CURRENT PATHWAY**

- Traditional Review Method

**PRE-CERT PATHWAY**

- Streamlined Review
- Excellence Appraisal

While maintaining reasonable assurance of safety and effectiveness, the paradigm today’s device world (Hardware-based) and digital health device world (Software-based) differ in their approaches to data collection and review methods.
2019 Test Approach

Excellence Appraisal
Pre-Cert team conducts excellence appraisal

Streamlined Review
Pre-Cert team identifies and extracts elements for SR

Review Team (Pre-Cert Pathway)
Review team makes a determination of reasonable safety and effectiveness based on review of the Excellence Appraisal results and the Streamlined Review elements

Pre-Cert Team
Evaluates and refines Pre-Cert Model based on the comparison of findings of both review teams

Traditional Review Method
Review team evaluates submission

Regulatory Decision
OHT Leadership makes the final regulatory decision on the product

DeNovo Premarket Submission
Pilot participant company submits a product for review.
Developing the Program with Stakeholder Input

All stakeholders

The FDA continues to seek input on the Pre-Cert working model from the public through the public docket. Your input will help shape the next steps that we take to build the Pre-Cert program.
Discussion Paper

A **TPLC** approach for modifications to Ai/ML

*Software as a Medical Device (SaMD)*
Artificial Intelligence & Machine Learning

Artificial Intelligence (AI)
Programming computers to perform tasks to mimic human capabilities—such as understanding language, recognizing objects and sounds, learning, and problem solving—by using logic, decision trees, machine learning, or deep learning.

Machine Learning (ML)
*Subset of AI* that gives “Computers the ability to learn without being explicitly programmed” -Arthur Samuel, 1959

- **Supervised Learning** (labeled data)
- **Unsupervised Learning**
- **Deep Learning** *Subset of ML*: enable computer to teach itself by exposing it to vast amount of data
- **Reinforcement Learning**
AI/ML-Based Medical Devices

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
Examples of AI/ML-Based SaMD

FDA News Release

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

February 13, 2018

FDA News Release

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

April 11, 2018
AI/ML-Based Medical Devices: Challenges

- Need for large, high-quality, well-curated data sets
- Explain-ability of these “black box” approaches
- Identifying and removing bias
Typical AI/ML Model Lifecycle

Good Machine Learning Practices

Data selection and management

Model training and tuning

Data for re-training

Model validation
  - Performance evaluation
  - Clinical evaluation

Model monitoring
  - Log and track
  - Evaluate performance

Data for re-training

New (Live) Data

Deployed Model

Legend
- AI Model Development
- AI Production Model
- AI Device Modifications

Locked Algorithm, Discrete Updates

SPECTRUM OF ML/AI-BASED ALGORITHMS

Updates less frequent and performed by human

Updates more frequent and performed by computer

Continuously Adaptive Algorithm

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FDA’s Proposed TPLC Approach Overlaid on AI/ML Workflow

Good Machine Learning Practices

Data selection and management

Model training and tuning

Model validation
- Performance evaluation
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Data for re-training

Culture of Quality and Organizational Excellence

New (Live) Data

Deployed Model

Model monitoring
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SPECTRUM OF ML/AI-BASED ALGORITHMS

Updates less frequent and performed by human

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Legend
- AI Model Development
- AI Production Model
- AI Device Modifications
- Proposed TPLC Approach

Premarket Assurance of Safety and Effectiveness

Review of SaMD Pre-Specifications and Algorithm Change Protocol

Real-World Performance Monitoring

Real-World Performance Monitoring

Culture of Quality and Organizational Excellence

AI Production Model

AI Device Modifications

Proposed TPLC Approach
"We’re building our Digital Health Center of Excellence to develop more efficient ways to ensure the safety and effectiveness of technologies like smart watches with medical apps. Our Software Precertification Pilot Program is allowing us to test a new approach for product review."

Dr. Scott Gottlieb, FDA Commissioner
April 2, 2019
Q&A