FDA Regulation of Artificial Intelligence

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Presenter Introduction

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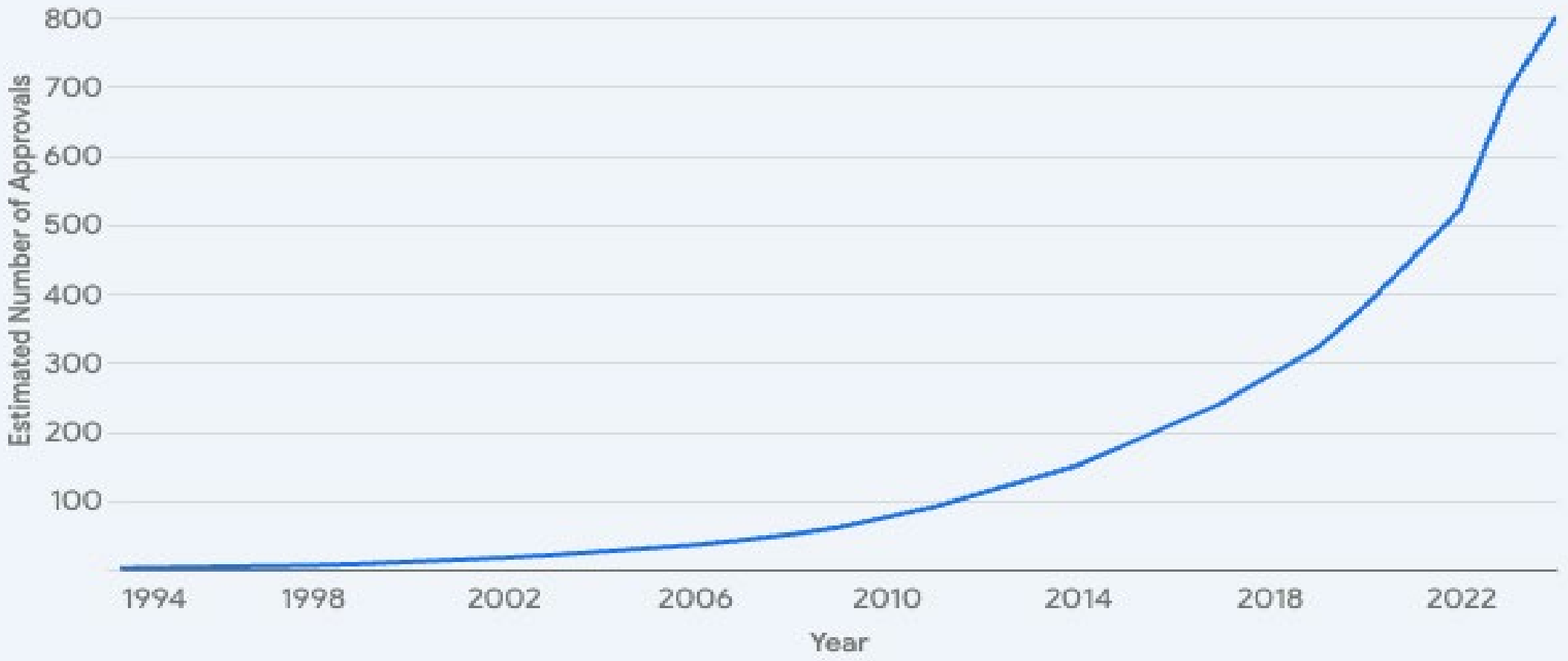
Nathan focuses his practice on FDA-regulated clients. His industry experience allows him to provide actionable legal advice on a variety of health law matters.

Nathan regularly advises FDA-regulated clients on regulatory and compliance matters. He advises clients on their advertising and promotion programs, represents clients in front of the FDA on a variety of matters, and assesses industry initiatives for compliance concerns. Nathan's extensive regulatory experience allows him to advise clients regarding a variety of medical products, including pharmaceuticals, medical devices, medical foods, and nutritional supplements.

Objectives

- What is Artificial Intelligence (AI)
- FDA Regulation of AI
- Challenges Associated with AI
- Partnering with FDA

FDA Approvals of AI Devices Over Time



Wearing FDA’S Shoes

- Artificial intelligence is exploding
- FDA follows a regulatory structure that was not made for AI
- FDA is trying to keep up with innovation while protecting public health

Artificial Intelligence / Machine Learning

- Artificial Intelligence (AI) has been broadly defined as the science and engineering of making intelligent machines, notably intelligent computer programs. AI can use techniques such as models based on statistical analysis of data, expert systems that primarily rely on if-then statements, and machine learning.
- Machine Learning (ML) is an AI technique that can be used to design and train software algorithms to learn from and act upon data.
  - Software developers can use ML to create an algorithm that is ‘locked’ so that its function does not change, or ‘adaptive’ so its behavior can change over time based on new data.

Why is AI/ML Important in Healthcare?

- AI and ML are used to derive new insights from the enormous amount of data generated during the delivery of healthcare.
- AI/ML can learn from real-world use and experience and can improve its own performance.
- Manufacturers are using AI/ML to innovate their products to assist healthcare providers and improve patient care.

- *AI is perhaps the most transformational technology of our time, and healthcare is perhaps AI's most pressing application.* -Satya Nadella, Microsoft CEO

AI/ML in Healthcare

- Predict post-surgical outcomes
- Remote Surgery
- Assist in diagnosing
- Help manage the almost overwhelming amount of data generated in the healthcare space
- Additional applications are a constant in this space

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FDA Regulation of Medical Devices

- The evolving nature of medical devices that employ AI/ML differentiate them in a meaningful way from traditional medical devices that are innovated in discrete generations, e.g., a single model or version of a device is improved upon and released as a new model or version.
- Traditionally, FDA reviews medical devices through an appropriate premarket pathway:
  - premarket clearance (510(k)),
  - De Novo classification, or
  - premarket approval.

510(k)

- Before marketing a device that has a legally marketed predicate device and that is not exempt from premarket notification (most class I and class II devices), each submitter must receive an order, in the form of a letter, from FDA which finds the device to be substantially equivalent (SE) and states that the device can be marketed in the U.S. This order "clears" the device for commercial distribution.
  - Class I: A low to moderate risk device requiring general controls.
  - Class II: a moderate risk device requiring general and special controls.
  - Class III: Devices that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury.

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510(k) Cont.

- Put differently, a 510(k) is a premarket submission made to FDA to demonstrate that the device to be marketed is as safe and effective, that is, substantially equivalent, to a legally marketed device. *See* section 513(i)(1)(A) FD&C Act.
- Submitters must compare their device to one or more similar legally marketed devices and make and support their substantial equivalence claims.

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Device Incorporating AI that Required a 510(k)

- Spinal implants have been used for some time to help with various spinal defects
- A lot of implants require customization based on patient measurements, age, etc.
- 510(k) clearance is required to market the implant
- Recently, AI has been utilized to predict the outcomes based on dimensions and location of implant
- Even with AI guiding the process, 510(k) utilizing a predicate is path to market clearance

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De Novo Classification

- A De Novo classification request is a marketing pathway utilized to classify novel medical devices for which general controls alone, or general and special controls, provide reasonable assurance of safety and effectiveness for the intended use, but for which there is no legally marketed predicate device. *See* section 513(f)(2) of the FD&C Act.
- Devices that are classified into class I or class II through a De Novo classification request may be marketed and used as predicates for future premarket notification (510(k)) submissions, when applicable.

Device Incorporating AI that Required De Novo 510(k)

- Device detects GI lesions
- Relies on advanced software algorithm
- Algorithm alerts when images contain potential lesions
- Due to mechanism of device (advanced software algorithm incorporating AI), predicate was not available

Premarket Approval

- Premarket approval (PMA) is the process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. *See* section 515 of the FD&C Act.
  - Class III devices are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury.
- PMA approval is based on a determination by FDA that the PMA contains sufficient valid scientific evidence to assure that the device is safe and effective for its intended use(s).

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Device Incorporating AI that Required a PMA

- Breast Imaging System
- Results in breast cancer diagnosis
- Risks due to misdiagnosis require a PMA under Product Code QNK
- Use of AI allows providers to differentiate between benign and malignant masses
- Similar use of AI as 510(k) products, but intended use plays a large role in classification

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Traditional Review for Device Modifications

- FDA reviews and clears modifications to medical devices, including software as a medical device, depending on the significance or risk posed to patients presented by the modification. *See* Deciding When to Submit a 510(k) for a Change to an Existing Device (Oct, 2017).
  - When applicable, the change in a medical device would trigger the requirement that a manufacturer submit a new premarket notification (510(k)) to the FDA.
- Under the traditional FDA regulatory framework, changes to software require new risk assessments to determine whether the change affects the functionality or risk category before releasing each change. That is, the algorithm is essentially locked and cannot change while out in the market, defeating the optimization of AI/ML technology.

Market Pathway Challenges

- Device Classification
- Intended Use
- Predicate Devices

AI/ML Changes

- While FDA has already approved, authorized, or cleared over 500 AI/ML devices, FDA continues to receive an increasing number of marketing submissions and pre-submissions for AI/ML-enabled medical devices. FDA's traditional approach for the regulation of hardware-based medical devices, however, is not well suited for the faster, iterative design and development, and type of validation used for software device functions, including Software as a Medical Device.
- FDA's traditional paradigm of medical device regulation was not designed for adaptive AI and ML technologies.

Typical 510(k) and PMA Devices FDA Historically Reviews

- PMA
  - Pacemakers
  - Neuromodulation
  - Implanted Drug Delivery Systems

- 510(k)
  - Ablation systems
  - Balloon dilation devices
  - Imaging navigation systems

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2019 Discussion Paper & 2021 Action Plan

- FDA outlined a Predetermined Change Control Plan for premarket submissions in its 2019 Discussion Paper and 2021 AI/ML-based Software as a Medical Device Action Plan, allowing manufacturers to predict algorithm changes and implement future modifications without requiring additional marketing submissions.
- Under a Predetermined Change Control Plan, manufacturers would be required to submit:
  - a detailed description of the specific, planned device modifications;
  - the methodology to develop, validate, and implement these modifications in a manner that ensures the continued safety and effectiveness of the devices; and
  - an impact assessment to assess the benefits and risks of the planned modifications and risk mitigations.

Draft Guidance

- On April 3, 2023, U.S. Food and Drug Administration (FDA) issued its much-anticipated draft guidance, “Marketing Submission Recommendations for a Predetermined Change Control Plan for Artificial Intelligence/Machine Learning (AI/ML)-Enabled Device Software Functions”
- The Draft Guidance built on the proposed framework and helped clarify the types of modifications that should be included in the Predetermined Change Control Plan.
- Notably, FDA also proposed that the Predetermined Change Control Plan articulated in the initial proposed framework be used for not only AI/ML-enabled Software as a Medical Device, but for all AI/ML-enabled device software functions, including software functions that are part of or control hardware medical devices.

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Benefits to Industry of Draft Guidance

- Better predictability for launch timing regarding new versions of an approved or cleared device
- Cost savings associated with less regulatory submissions
- Allows for patients to realize benefits of aggregated data sooner

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Draft Guidance Cont.

- FDA expects manufacturers to commit to transparency and real-world performance monitoring, and to periodically update FDA on changes implemented as part of the approved pre-specifications and algorithm change protocol.
- In addition, modifications should be implemented following appropriate, well-defined practices, such as the Good Machine Learning Practice guiding principles jointly developed by FDA, Health Canada, and the United Kingdom’s Medicines and Healthcare products Regulatory Agency.

Draft Guidance Cont.

- The Draft Guidance seeks to enable manufacturers to market medical devices with continuously learning algorithms without having to obtain a new authorization or clearance for each change, so long as the changes are in line with the predetermined plan.
- Through this Draft Guidance, FDA seeks to provide flexibility for devices with continuously learning algorithms, while retaining certain limits on the software to safeguard continued safety and effectiveness of the devices.

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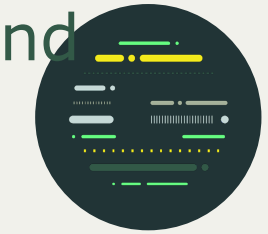
Implementing the Draft Guidance

- Consider this guidance in the development of your product
- Clearly lay out your PCCP in your pre-market submissions and be prepared for deficiencies
- Ensure post-market team is aware of and understands the PCCP
- If post-market changes result in a submission, consider whether an update to the PCCP is also needed
- Clear communication with your team and with FDA will allow realization of benefits discussed above

When is SaMD Subject to FDA Oversight?

- In the digital health context, we see robust innovation in AI/ML in the context of clinical decision support software (CDS).
- FDA has long regulated software that meets the definition of a device (section 201(h) of the FD&C Act), including software that is intended to provide decision support for the diagnosis, treatment, prevention, cure, or mitigation of diseases or other conditions.
- CDS is described as a variety of tools, e.g.: computerized alerts and reminders for providers and patients; clinical guidelines; condition-specific order sets; focused patient data reports and summaries; documentation templates; diagnostic support; and contextually relevant reference information.



21st Century Cures Act

- In 2016, Congress narrowed the scope of software potentially subject to FDA regulation by enacting Section 3060 of the 21st Century Cures Act, which amended Section 520(o) of the FDCA to exclude certain medical software functions, including certain CDS software, from the definition of a device.
- Pursuant to Section 520(o)(1)(E) of the FDCA, CDS software is excluded from the definition of a device if it meets all four of the following criteria:
  1. Is **not** 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 (Criterion 1);

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21st Century Cures Act Cont.

2. is intended to display, analyze, or print medical information about a patient or other medical information, like clinical practice guidelines (Criterion 2);
3. is intended to support or provide recommendations to an HCP about prevention, diagnosis, or treatment of a disease or condition (Criterion 3); **and**
4. is intended to enable HCPs to independently review the basis for the software's recommendations so HCPs do not primarily rely on the recommendations when making a clinical diagnosis or treatment decision (Criterion 4).

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CDS Guidance

- On September 28, 2022, FDA issued final guidance on CDS, which significantly amending the interpretive framework for CDS software regulation it had proposed in a revised draft guidance issued on September 27, 2019.
- The CDS Final Guidance focuses on explaining how FDA interprets the statutory criteria that exclude a software product from the definition of a medical device, which FDA has termed “Non-Device CDS.”

Criterion 1 & 2

- Criterion 1: Any software that uses a medical image (e.g., CT, MRI, or X-ray image), a signal from an in vitro diagnostic (IVD) as an input, or a pattern/signal from a signal acquisition system that measures a parameter from within, attached to, or external to the body for a medical purpose (e.g., an electrocardiogram) would fail Criterion 1 and be classified as a regulated medical device.
- FDA explains that Criteria 1 and 2 together describe the types of data inputs used in device CDS (Criterion 1) and non-device CDS (Criterion 2).
- Software that fails on Criterion 1 (i.e., is intended to acquire, process, or analyze a medical image or a signal) would necessarily fail on Criterion 2.

Criterion One Example

- A device that enhances an MRI image to assist the HCP reviewing the scan would likely fail this criterion

- A device that merely stores an MRI image for access may likely meet this criterion

Criterion 2

- FDA explains that "medical information about a patient" refers to the type of information typically communicated between HCPs in a clinical conversation or between HCPs and patients in the context of a clinical decision, meaning the relevance of the information to the decision-making is "well understood and accepted." FDA interprets "other medical information" to include information such as peer-reviewed clinical studies, clinical practice guidelines, and information that is independently verified and validated as accurate, reliable, not omitting material information, and supported by evidence.
- Criterion 2 would exclude potentially relevant information that is not yet "well understood and accepted," limiting the type of inputs that can be used by non-device CDS software functions.

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Criterion 2 Example

- Real-time monitoring of a patient's glucose level would likely fail this criterion

- Displaying a patient's glucose level taken in a lab would likely meet this criterion

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Criterion 3

- FDA asserted that software must satisfy the following four conditions to qualify as non-device CDS:
  - It provides condition-, disease-, and/or patient-specific information and options to an HCP to enhance, inform and/or influence a health care decision;
  - It does not provide a specific preventive, diagnostic, or treatment output or directive;
  - It is not intended to support time-critical decision-making; and
  - It is not intended to replace or direct the HCP's judgment.
- FDA asserts that software that provides information that a specific patient "may exhibit signs" of a disease or condition or identifies a risk probability or risk score for a specific disease or condition would fail under the third criterion and be regulated as a medical device.

Criterion 3 Example

- Software that takes glucose levels of a patient as an input and then suggests a course of action (provide X medication at Y dose) would likely fail this criterion

- Software that displays the glucose levels of a patient and then displays a scientifically valid range of normal glucose levels would likely meet this criterion

FDA Rationale

- FDA's rationale for these new conditions turns on the concept of automation bias (i.e., the tendency for over-reliance on an automated system).
- Automation bias is more likely, according to FDA, to occur if the software provides a single, specific output rather than a list of options or complete information for the HCP's consideration.
- Similarly, time-critical decision-making results in automation bias because the user does not have sufficient time to adequately consider other information.
- Thus, the greater the software automation and time-critical nature of the decision-making, the more likely the HCP will be to accept the identified software output as the best course of action and less likely to seek additional information to inform decision-making.

Criterion 4

- The CDS Final Guidance includes several tangible recommendations on satisfying this criterion. FDA recommends that software or labeling do the following:
  - Include the purpose or intended use of the product, including the intended HCP user and patient population;
  - Identify the required medical inputs with plain language instructions on how the inputs should be obtained, their relevance, and data quality requirements;

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Criterion 4 Cont.

- Provide a plain language description of the underlying algorithm development and validation that forms the basis for CDS implementation, which would include a summary of the logic or methods used, the underlying data relied upon, and the results from clinical studies used to validate the algorithm/recommendations; and
- Provide, in the software output, patient-specific information and other knowns/unknowns, such as corrupted or missing data, to enable the HCP to independently review the basis for the recommendations and apply their own judgment.

- FDA opines that in some cases, usability testing may be necessary to determine whether implementation of CDS software meets the fourth criterion

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Criterion 4 Example

- Software that provides a normal glucose level range for a patient but that does not disclose the rationale behind the provided range, such as the patient population, would likely fail this criterion

- Software that provides a normal glucose level range and discloses the rationale behind the range and any literature relied upon that allows the HCP to determine whether the range is applicable to their patient would likely meet this criterion

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FDA Provided Examples

- FDA states that a software function that analyzes glucose measurements from a continuous glucose monitor every 30 minutes and notifies the patient's HCP of potential hypoglycemia is a device function because it analyzes a pattern (failing Criterion 1), is not intended to display, analyze, or print medical information (failing Criterion 2), and provides a specific diagnostic output and supports time-critical decision-making (failing Criterion 3).
- Software that identifies patients with a possible diagnosis of opioid addiction based on analysis of patient-specific medical information, family history, prescription patterns, and geographical data does not meet Criterion 3 because it provides a specific diagnostic or treatment output or directive.

AI is Complex…

- What are the major issues:
  - Laws and regulations lag behind
  - Device classification
  - Proving safety and efficacy
  - Post-market
  - Advertising and promotion

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How to Mitigate Device Risks

- Software development
  - Quality system
  - Avoid shortcuts
- Cybersecurity
  - FDA guidance
  - Proactive
- Physician Reliance
  - 510(k)
  - De Novo
  - PMA
- FDA Oversight
  - FDA review takes time
  - Avoiding FDA may result in an adulterated device

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FDA Communication Strategy

- Pre-submission Options
  - Informational pre-submission
  - Option to start dialogue early
  - FDA will be in “listening mode”

- Pre-submission to clarify issues
  - IDE
  - Pre-market submissions

- Other opportunities
  - Requests for designation
  - 513(g)
  - Administrative Questions
  - Ongoing discussing during submission review

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FDA Communication Considerations

- Be honest (obviously)
- Know what you know … and what you don’t
- Be on the same page with your team
- Take advantage of every opportunity
- Do not fear FDA

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Post-Market Considerations

- Change Control
- Claims Development
- Real-World Evidence

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Government Acknowledges AI’s Importance

AI Executive Order

- Artificial intelligence (AI) holds extraordinary potential for both promise and peril. Responsible AI use has the potential to help solve urgent challenges while making our world more prosperous, productive, innovative, and secure.

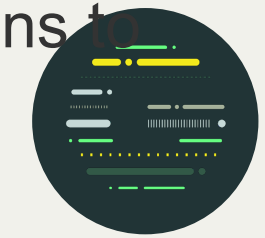
- Harnessing AI for good and realizing its myriad benefits requires mitigating its substantial risks. This endeavor demands a society-wide effort that includes government, the private sector, academia, and civil society.

Robert M. Califf, M.D., Commissioner of Food and Drugs

March 5, 2024:

- As you understand, our biomedical science, clinical and public health enterprises are ripe with achievement today, but we are on the verge of revolutionary change.

- My concern is that our health systems do not have the infrastructure and tools to make the most important determinations about whether an AI application is “effective” for health outcomes. In order to know whether an algorithm of any kind is truly effective for health, we need two conditions to be supported with a functional infrastructure.



Digital Health Center of Excellence

- FDA program designed to
  - Connect and build partnerships
  - Share knowledge
  - Innovate regulatory approaches

In Closing

- AI is complex and FDA is using pre-AI processes to evaluate
- Companies want to take advantage, but beware
- Partner with FDA

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Questions

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Thank you!

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