Innovation Centre of Denmark
US Market Entry & FDA Requirements

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CODE OF FEDERAL REGULATIONS

CFR

OFFICE OF THE FEDERAL REGISTER

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Craig J. Coombs, RAC

- Regulatory Affairs Certified
- BS Biology – Stanford University

- Regulatory Affairs Specialist since 1989

- Serially acquired by Medtronic in 5 startups

- Vice President of Regulatory, Quality & Clinical Affairs in MDT subsidiary

- President, Coombs Medical Device Consulting, Inc since 1999

- Instructor, University of California at Santa Cruz, Medical Device Submissions since 2006

- Board of Advisors
  - Magnetic Particle Imaging
  - Nyquist Data

Agenda

1. Why you need a Regulatory Plan. What it contains.

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Agenda

1. Why you need a Regulatory Plan. What it contains.

2. High level look at US Regulations you need to know to discuss entering the US.

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3. Testing needed to support your submission.

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2. High level look at US Regulations you need to know to discuss entering the US.

3. Testing needed to support your submission.

4. How FDA is regulating software as a medical device (SaMD) and in a medical device (SiMD).

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FDA PreSub

Reimbursement

Clinical Study

Device Concept

Reimbursement=

Being paid the amount

you have predicted

for the Indications for Use

you want

Indications for Use:

Your claim of what the device can do

for a health problem

for a certain type of patient

in a specified use environment.

Rush Bennet BioDesign methodology for **needs statement:**

A way to ... **Problem**.... for a specific ... **Population**.... in order to achieve a specific and measurable ... **Outcome**

This should be very similar to your Indications for Use statement when designing medical devices.

- Typical Payers in the US
  - Government
  - Insurance
  - Private Payer

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- # Reimbursement specialist
  - ## Kuo Tong: Kuo.Tong@Navigant.com

What can you learn

from a good regulatory plan?

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+

- Regulatory Plan will tell you the timing and need for
  - Presubmission negotiations
  - Biocompatibility & bench testing
  - Clinical testing
  - Regulatory pathway
  - FDA or Advisory Committee meetings
  - Guess at post market studies, if necessary

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FDA PreSub

Reimbursement

Clinical Study

Device Concept

Informed guesses as to time and cost to each milestone =

Knowledge of amount of money you need and when you need to raise it to achieve a revenue goal or buyout price=

Return on Investment (ROI) or Internal Rate of Return (IRR) for your investors

ROI or IRR are what sets company premoney valuation.

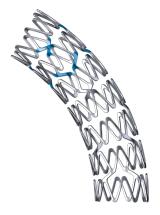Sets founders proportion of payout.

US Regulatory Pathways

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- Research Use Only
- Analyte Specific Reagent
- Investigational Use Only
- Humanitarian Device Exemption
- Custom Device
- Premarket Approval (PMA)
- PMA Supplement (7)
- Only non-medical claims (Wellness devices & 21st Century Act devices)
- Biological License App

- Traditional 510(k) (Premarket Notification)
- Special 510(k)
- Abbreviated 510(k)
- Safety & Performance 510(k)
- *de Novo* 510(k)
- 510(k) Exempt
- "Enforcement Discretion"
- Private Label
- Letter to File
- Kitting

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- 6 common regulatory pathways
  - Premarket Approval (PMA)
  - Premarket Notification (510(k) clearance)
  - 510(k) Exemption
  - de *Novo*
  - Software as a Medical Device (SaMD)
    - Enforcement Discretion
    - Not a medical device

US Regulatory Classification Scheme:
Class III: Highest Risk

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- Class III devices require a Premarket Approval (PMA) before entering US market

- PMA must contain adequate information that the device is Safe and Effective at meeting its claims (i.e., Indications for Use)

- Typically has prospective clinical study data.

- PMA time to approval = 180 days after submission of clinical data.

Class II: Moderate Risk Devices

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- Class II devices require a Premarket Notification (510(k)) clearance before entering US market

- 510(k) must demonstrate that the new device is "Substantially Equivalent" to a "Predicate" 510(k) cleared device

- Only 10-15% of submission have clinical data.

- 510(k) time to clearance = 90 FDA review days.

- Due to review clock stoppage when Additional Information is required, 510(k) clearance time = ~135 calendar days.

- ## Substantial Equivalence

  A device is substantially equivalent if, in comparison to a predicate it:

  – has the same intended use as the predicate; **and**

  – has the same technological characteristics as the predicate;
    OR

  – has the same intended use as the predicate; **and**

  – has different technological characteristics and the information submitted to FDA;

    - does not raise new questions of safety and effectiveness; **and**

    - demonstrates that the device is at least as safe and effective as the legally marketed device.

Intended Use ≠ Indications for Use

- Most recent definition of Intended Use:

"the general purpose of the device – or what the device does – and encompasses the indications for use."

"the term "Indications for Use" describes the disease or condition the device will diagnose, treat, prevent, cure or mitigate, including a description of the patient population for which the device is intended."
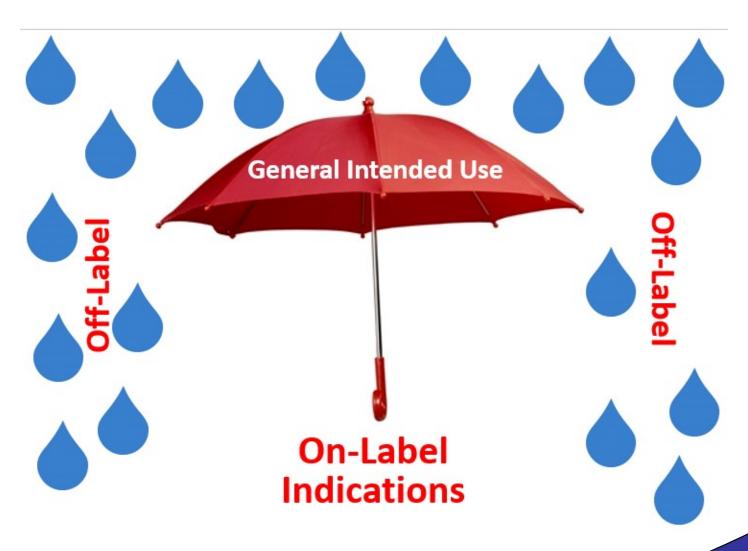
General Intended Use

Off-Label

Off-Label

Tool Use

Peripheral

Ablating

Cardiac

Neuro

On-Label Indications

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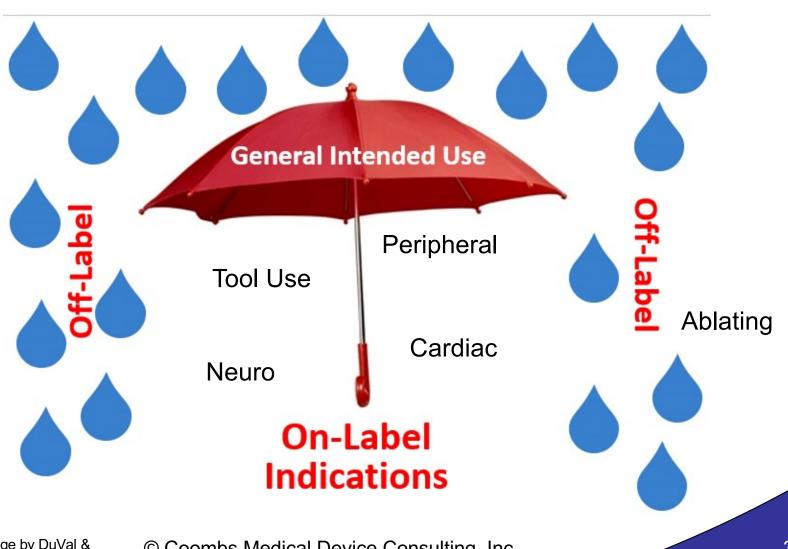
Class I: Lowest Risk Devices

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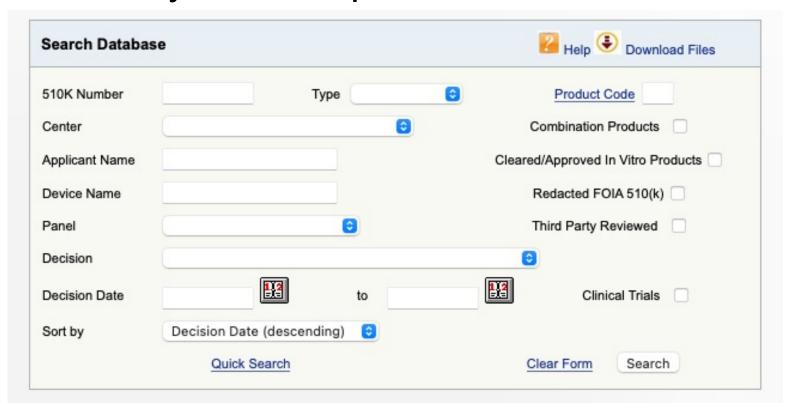## *US Market Entry & FDA Requirements*

- Most, but not all, Class I devices are 510(k) exempt. Some Class II devices are also 510(k) exempt.

- You should still complete most elements of the 510(k), including the SE Justification.
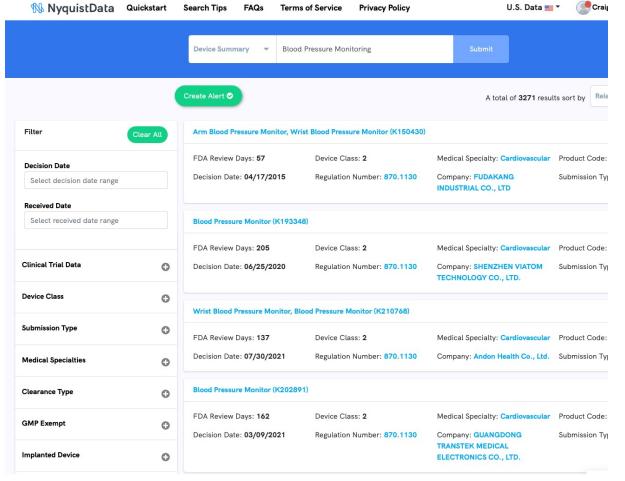
- File only in your internal file.

- 510(k) exempt devices must still follow regulations concerning:
  - Registration & Listing
  - Corrections and Removals
  - Labeling
  - Good Manufacturing Practices (many Class I devices are exempt from GMP)
  - Design Control (if Class II)

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- How do you find a predicate device?

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm

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- Use AI to search entire FDA database.

WWW.NyquistData.com

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- An AI search engine will allow rapid determination of
  - Predicate devices
  - Product Codes
  - Testing required by FDA
  - Previously cleared Indications for Use

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The advantages of an AI/ML-enabled search engine for FDA records

The FDA's new list of artificial intelligence and machine learning-enabled devices highlights opportunity for improvement.

(Image courtesy of the FDA)

*Craig Coombs and Qiang Kou, **Nyquist Data***

https://www.massdevice.com/fda-devices-artificial-intelligence-machine-learning-list-nyquist-data/

- What if no predicate can be found, and yet you are able to demonstrate that your device should be considered a Class II or I?

- *de Novo* Submissions
  – Can have extensive data burden because you must prove safety and effectiveness
  – Most have clinical trial data
  – FDA review days = 120, Actual calendar days closer to a year to accommodate FDA queries
  – Subsequent filings can use your *de Novo* as a predicate, but must do same testing as your *de Novo*.

- How do I determine the testing necessary to support a submission?
  - Support your claims
  - Probably be similiar to predicate (Don't test predicate).
  - Check for relevant standards

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Source of potential testing requirements

- Known, documented clinical need or requirement
- Standards (EN, ISO, AAMI, ASTM, Military, BSI, DIN, etc.)

  1. Harmonized standards
  2. Nonharmonized European Standard
  3. International Standard
  4. National Standard
  5. Specific National Guidance (e.g., FDA, MEDDEV guidances)
  6. Industry Standard (e.g., substantial equivalence with what's already used in medical community)
  7. Qualified (i.e., validated) Company Standard

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Source of potential testing requirements

8. General Guidelines (e.g., FDA)
9. Predicate claims
10. Last three years of 510k summaries for same procode
11. Similar PMA'd devices
12. Labeling Claims
13. MAUDE Database
14. Medical Literature
15. Risk Analysis
16. Pre-Submission meeting
17. FDA-Industry meeting

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- PreSubmission Guidance
  - PreSub mtg (When it's critical to have input)
  - PreIDE mtg (IDE=Investigational Device Exemption, necessary for clinical study in US)

Software as a Medical Device (SaMD)

Software in a Medical Device (SiMD)

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- Different types of healthcare related software (SW)
  - Associated with hardware
    - SW in a medical device
    - SW in a wellness device
  - "Stand alone" software
    - SW that isn't a medical device
    - SW that is probably a medical device, but FDA doesn't care
    - SW that is a medical device
    - SW that is a medical device, but now the law says it isn't
    - SW that the law says is NOT a medical device, but the FDA says it is.

- SiMD: Does it run the device?
  - Is it integral to a medical device?
    - Pacemaker
    - IVD analysis system
    - RF Generator

- ## SiMD: Critical to Indications?

  - ### Is it an accessory to a medical device?

    - Image analysis

    - Arrhythmia detection

    - Medical device programmer

    - Optional device automation

- ## Software in a "Wellness Device"

  - Typically have a sensor for a physiological monitoring (spot-checking or continuous)

  - Intended for healthy people in health promoting activities

  - Not intended to detect unhealthy condition (exception: fall detection)

    - Heart Rate

    - Oximeters

    - Respiratory rate monitors

Stand alone software
SaMD

- **SW that is not a medical device** (examples)
  - Clinical & disease reference info
  - Surgical training videos
  - General purpose health training, patient educ
  - Clinical simulation SW
  - Electronic Health Records

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- Software that MAY BE a medical device (enforcement discretion due to low risk)
  - video and video games to motivate patients to do their physical therapy exercises at home
  - checklist of common signs and symptoms to provide a list of possible medical conditions and advice on when to consult a health care provider
  - Mobile apps that display, at opportune times, images or other messages for a substance abuser who wants to stop addictive behavior
  - provide the surgeon with a list of recommended intraocular lens powers based on information inputted by the surgeon

- Medical Mobile Apps that are medical devices
  - software meets the definition of a device under section 201(h) of the FD&C Act and its functionality poses a risk to a patient's safety if the software were to not function as intended.

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- Apps that will be regulated as Medical Devices
  - Apps that transform a mobile platform into a regulated medical device
  - Apps that connect to an existing device type for purposes of controlling its operation, function, or energy source

- MMA medical device examples
  - SW that controls a medical device (adjust infusion pump)
  - SW connected to sensor that measures some physical parameter (ECG, EEG, SpO2 for disease)
  - SW that makes (e.g., smartphone) camera or microphone or speaker act like a medical device.

- If your device is class III, then so are its accessories*, and then any associated software accessories will probably be regulated as a medical device.

- SW that has been a medical device, but now the law says it isn't
  - 21st Century Cures Act (Dec 2016)
    - Medical Device Data Systems (MDDS)
    - Medical Image Storage Devices
    - Medical Image Communications Devices
  - Clinical Decision Support Software

  Draft guidelines out Sept 2019

  https://www.fda.gov/media/109618/download

- # Clinical Decision Support Software (CDS)

(1) 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

(2) Intended for the purpose of displaying, analyzing, or printing medical information about a patient or other medical information

(3) Intended for the purpose of supporting or providing recommendations to an HCP about prevention, diagnosis, or treatment of a disease or condition

(4) Intended for the purpose of enabling an HCP to independently review the basis for the recommendations that such software presents so that it is not the intent that the HCP rely primarily on any of such recommendations to make a clinical diagnosis or treatment decision regarding an individual patient

- CDS not as clear-cut as law states. CDS eligibility under the law is constrained by risk guidelines of the International Medical Device Regulators Forum (IMDRF).

- Therefore, if the risk of the CDS is high enough, then SW is not a medical device according to the law, but it is according to the FDA (even though risk is not a criteria under the 21st Cent Cures Act)

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New Guidelines since 2019

General Wellness: Policy for Low Risk Devices

https://www.fda.gov/media/90652/download

Policy for Device Software Functions and Mobile Medical Applications

https://www.fda.gov/media/80958/download

Medical Device Data Systems, Medical Image Storage Devices, and Medical Image Communications Devices

https://www.fda.gov/media/88572/download

Clinical Decision Support Software

https://www.fda.gov/media/109618/download

Policy for Device Software Functions and Mobile Medical Applications

https://www.fda.gov/media/80958/download

Documentation Necessary for SW Clearance/Approval

Content of Premarket Submissions for Device Software Functions

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on November 4, 2021.

https://www.fda.gov/media/153781/download

Basic Documentation

OR

Enhanced Documentation (includes basic)

Based on level of concern

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- # Documentation Requirements for Software
  - ~~Level of Concern~~
  - Documentation Level Evaluation - NEW
  - Software Description
  - System and Software Architecture Design Chart
  - Risk Management File (FTA, FMEA, HACCP, see TIR57)
  - Software Requirement Specification (SRS)
  - SW Design Specification (SDS)
  - ~~Traceability Analysis~~
  - Development procedures or IEC 62304 Conformity

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- Requirements for Software – cont.
  - Validation and Verification Testing
    - Unit, integration & system level
    - Black Box & White Box
    - Look for problems
  - Revision History Log
  - Unresolved Anomalies (i.e., bugs, defects, or errors)
  - ~~Release Version Number~~
  - **Run-Time Error Analysis**
  - **Cybersecurity Mitigations**

- Pertinent FDA Guidelines
  - Guidance on Content of Premarket Submissions for Device Software Functions (4 Nov 2021):
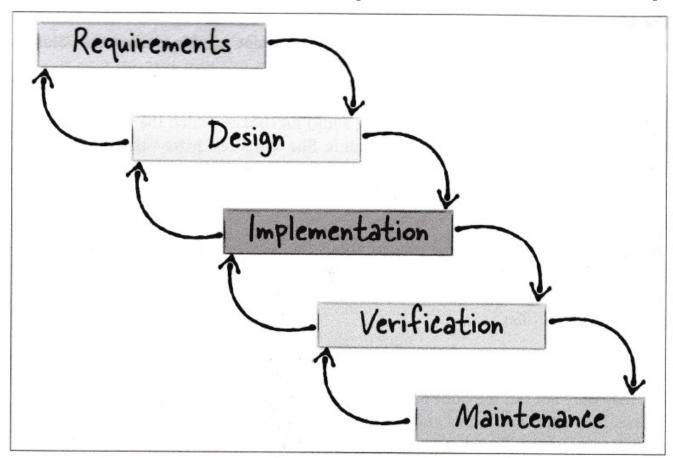   https://www.fda.gov/media/153781/download
  - General Principles of Software Validation:
    https://www.fda.gov/media/73141/download

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- Guidance for Off-the-Shelf Software (Sep 2019)
  https://www.fda.gov/media/71794/download

- Postmarket Management of Cybersecurity in Medical Devices (Dec 28, 2016)
  https://www.fda.gov/media/95862/download

- Pay attention to ISO 62304: Medical device software -- Software life cycle processes

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- Software device development
  - Waterfall
  - Agile

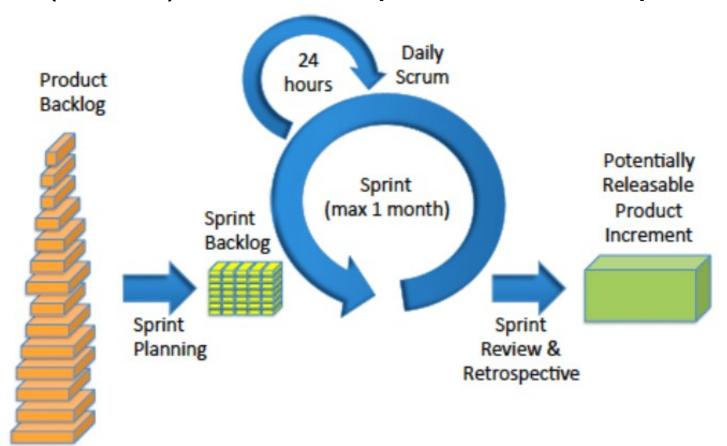- # Waterfall method of product development

Issues w development models:

Waterfall: rigid, requires up-front specs, regression difficult. Basis for FDA SW rqmnts written in 1990's.

Not used in SW development.

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- Agile (scrum) method of product development

Issues w development models:

Agile: Sometimes is poorly documented or doesn't produce requirements called out in FDA Gdlns or IEC 62304.

Both need Architecture, Risk Mitigation, and System validation, HW interface specs

AAMI TIR 45:2012: *Guidance on the use of AGILE practices in the development of medical device software*

Artificial Intelligence (AI)

Machine Language (ML)

- Artificial Intelligence (AI)
  - the science and engineering of making intelligent machines, especially intelligent computer programs (McCarthy, 2007). Artificial intelligence can use different techniques, including models based on statistical analysis of data, expert systems that primarily rely on if-then statements, and machine learning.

- **Machine Learning** is an AI technique that can be used to design and train software algorithms to learn from and act on data. Software developers can use machine learning 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.

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- **<u>Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD)</u>** https://www.fda.gov/media/122535/download
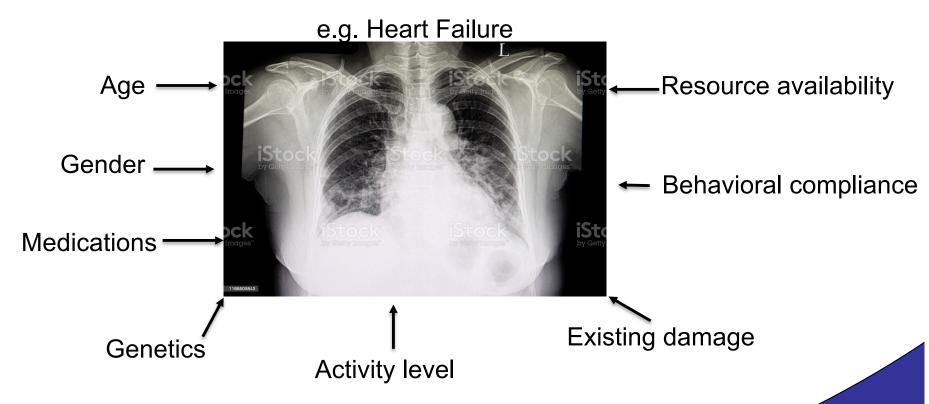
- **Artificial Intelligence and Machine Learning (AI/ML) Software as a Medical Device Action Plan** https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-software-medical-device

- FDA comfortable with AI/ML where the results can be compared to experts, or another "gold standard."
  - Radiographic tumor detection
  - Bone breaks
  - Dermatology assessments/screening

What about Multi-factorial diseases

without a Gold Standard Treatment?

e.g. Heart Failure

Age

Gender

Medications

Genetics

Activity level

Existing damage

Behavioral compliance

Resource availability

Even if you can "successfully validate", remember

Lily Peng's* common AI MYTHS:

– More data is all you need for a better model.

– An accurate model is all you need for a successful product.

– A good product is sufficient for clinical impact.

*Lily Peng, MD, Google Healthcare Product Manager, Google's Approach to HealthTech webinar, Oct 28, 2021

- Types of bias faced in AI clinical trials
  - Confirmation bias
  - Training set bias
    - Insufficient for a gender
    - Flawed for minority groups
  - Model Bias
  - Privacy concerns in de-biasing
  - Datasets mimic societal bias
  - AI typically amplifies bias

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- Pro Tip?
  - Save AI claims for marketing, especially if you have "locked" algorithms.

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- # Summary
  - Software adherence to regulation is not in accordance with standard development practices. However, compliance is evolving.
  - Issues of AI validation are vexing to industry and regulators.

- Summary

  – Many different ways to enter the US market. You decide based upon your device's classification and where it is on the development cycle

  – Typically your selection of Predicates and your Testing scheme are keys to success.

- # Summary

  - A regulatory plan is essential to reaching reimbursement at the earliest and least costly point.

  - The regulatory plan is a living document, to be altered when revisions to the device are necessary.

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THANK YOU

Danish Consulate General

Innovation Center, Silicon Valley

Siliconvalley.um.dk

Regulatory Information AI Search Engine:

www.NyquistData.com

Zoom Room Design:

www.ShelleyGoldenStyle.com

https://www.linkedin.com/in/shelleyegolden/