U.S. Regulatory Update

Chemical Angel Network

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AliraHealth

FDA

Regulatory Affairs Update

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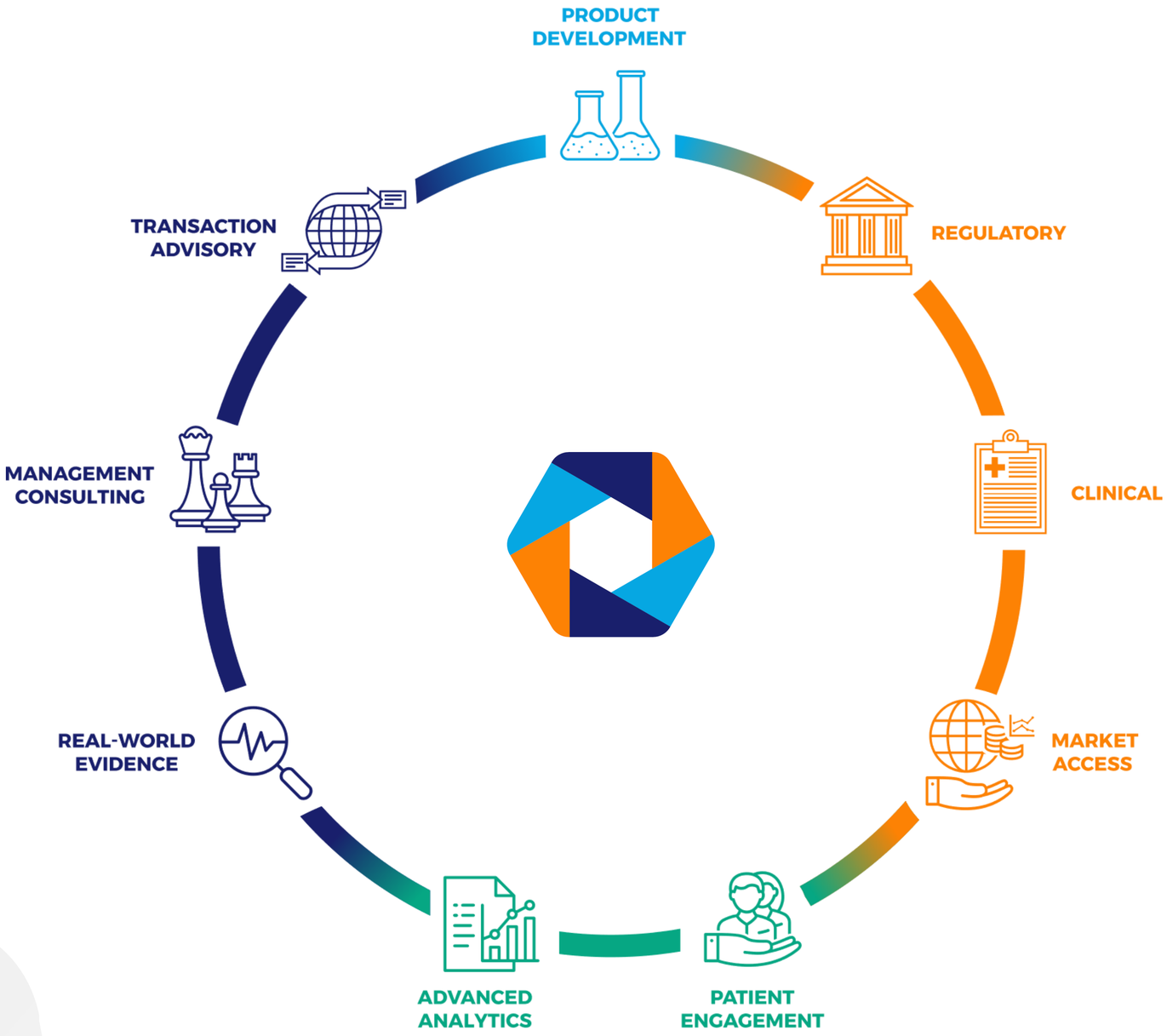
A Lifecycle Approach

We provide a variety of services under the same umbrella and with a **holistic approach** and clear vision: to offer **unparalleled support and value** at every stage of your corporate and product evolution.



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Our Practice Areas

PRODUCT DEVELOPMENT

IP Development (StructuredIP™)

Alira Health Ventures: Incubation of Breakthrough Technologies

In-VITRO and In-VIVO Testing

CMC Manufacturing Strategy and Operations

CMC Process Development and Optimization

CMC Outsourcing Support

CMC GMP Facility Design

CMC Project Integration

CMC Technical & GMP Training

REGULATORY

Strategy and Roadmap Development

Submission Management

Regulatory Framework Navigation

Health Authority Interactions

FDA and EMA Liaison Officer for Foreign Companies

Lifecycle Maintenance Support

CMC Quality and Regulatory Affairs

CLINICAL

Study Design and Protocol Writing

Site Selection and Feasibility

Investigator Training

Subject Recruitment & Retention

Data Management and Biostatistics

Trial Management and Clinical Operations

Pharmacovigilance

MARKET ACCESS

Global Market Access, Pricing and Reimbursement Strategy

Mock Negotiations and Payer Consultations

Health Economics and Outcomes Research Strategy

Real World Evidence Strategy and Plan

Value Communication

Value Based Healthcare Pilots

Market Access Diagnostic MAP™

Accelerated Coverage Pathways for Innovation

Indication Prioritization

Our Practice Areas

MANAGEMENT CONSULTING

- Market Opportunity Assessment
- Portfolio Management
- Commercial / Vendor Due Diligence
- Commercial Excellence
- Corporate Strategy Planning
- Commercial Strategy and Go-to-Market Model Development
- Integrated Launch Planning
- Healthcare Optimization

REAL-WORLD EVIDENCE

- Data Strategy
- Real-World Studies
- Real-Time Data

TRANSACTION ADVISORY

- M&A Sell-Side
- M&A Buy-Side
- Business Development and Licensing
- Carve-Out

ADVANCED ANALYTICS

- Data Analytics for Commercial Effectiveness
- Patient Journey and Behavior Analysis
- Parallel Trade Management

PATIENT ENGAGEMENT

- Patient Care Matrix
- Patient Knowledge Center
- Patient Advisory Board
- Patient Mobilization Program

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Alira Health at a Glance

Proactive. Success driven. International reach. We deliver excellence for every aspect of your transaction.

Since 1999, Alira Health's Transaction Advisory Team has been fully dedicated to increasing value for its clients; conducting assignments **from early-stage to commercial stage assets** and **companies** in **Pharma, BioTech** and **MedTech**; and benefits from the **expertise of all Alira Health practices**.

- **A lifecycle approach** to Life Sciences products, technologies, and services, from creation to commercialization
- **In-house laboratory, regulatory, CRO, and market access expertise**
- **Exclusively healthcare focused with expertise across the healthcare ecosystem**, from suppliers, payers and provider to patients
- Ability to combine **M&A/Investment-Banking processes & methodologies** with **scientific & strategy** driven perspective to best value Companies, Assets and Innovations

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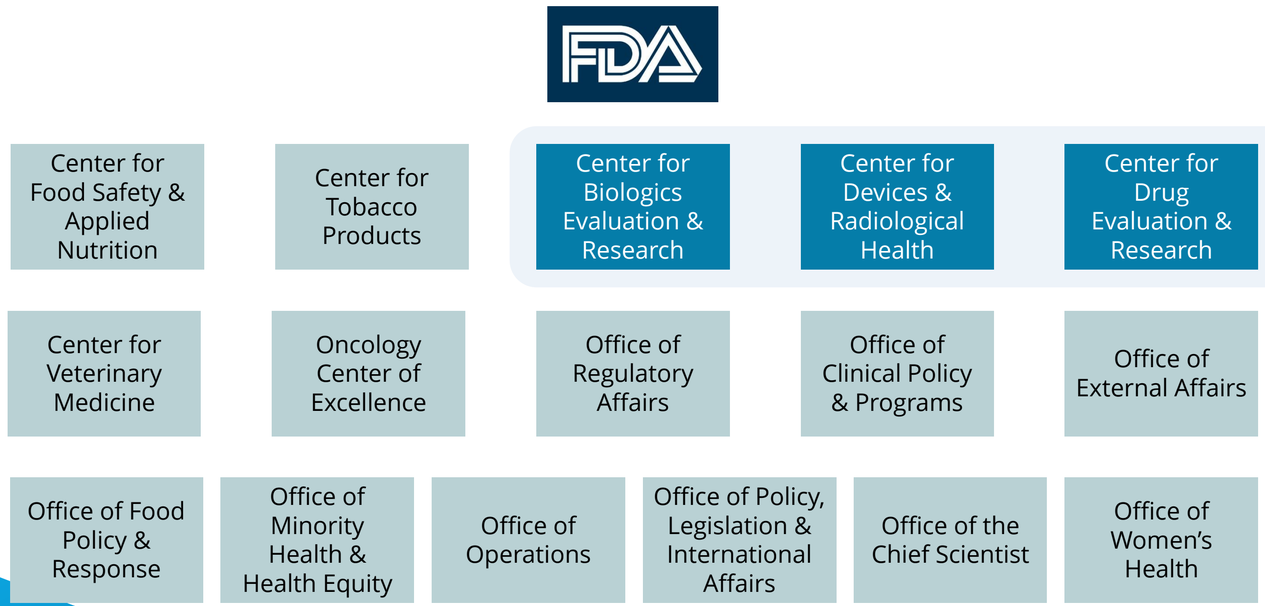
The FDA

The FDA is the federal agency regulating all medical products in the US. Every new medical product should be authorized for use by one of the FDA's entities, according to the product's type.

- The Food and Drug Administration (FDA) is a federal agency within the Department of Health and Human Services. It is responsible for:
  - Protecting the public health by **assuring the safety, effectiveness, quality, and security of human and veterinary drugs, vaccines and other biological products, and medical devices.** The FDA is also responsible for the safety and security of the United States' food supply, all cosmetics, dietary supplements and products that give off radiation.
  - Regulating tobacco products.

FDA Organization

The FDA is organized in several entities, each referring to a certain type of product. In July 2019, the FDA entities were[1]:



Focus on 3 Entities Regulating Drugs & Medical Devices

Center for Drug Evaluation and Research (CDER)

- The CDER regulates **over-the-counter and prescription drugs**, including **biological therapeutics and generic drugs**.

Center for Biologics Evaluation and Research (CBER)

- The CBER regulates **biological** and related products including **blood, vaccines, allergenics, tissues, and cellular and gene therapies**.

Center for Devices & Radiological Health (CDRH)

- Responsible for the **premarket approval of all medical devices**, as well as overseeing the **manufacturing, performance and safety** of these devices.
- Also **oversees the radiation safety performance of non-medical devices** which emit certain types of electromagnetic radiation, such as cellular phones and microwave ovens.

- Note: [1]The FDA is currently reshaping its internal organization and entities. Source: FDA.

FDA Regulatory Pathways Overview (1/2)

Clinical and Regulatory Strategy

The scenario choice will determine which program should be prioritized. Imaging device software and imaging drugs (e.g. contrast agents) if commercialized together are classified as a combination product by the FDA.

FDA Guidance on Contrast Agents and Software

- Specific guidance outlines **imaging device software** and hardware engineering technologies that utilize **imaging drugs**.
- The use of a diagnostic imaging device and imaging drug may constitute a **combination product when commercialized together or "cross labeled"**
- The FDA decides on the device class and responsible lead center in accordance with their **primary mode of action** mechanism.

	Request for Designation (RFD)	Pre-Submission
Product Designation	None	Medical Devices/Combination Product
Definition	Document submitted to FDA to determine: ▪ The classification of a product as a drug, device or combination product. ▪ Which FDA center[1] will have primary jurisdiction for combination product.	▪ Formal written request from an applicant when FDA the feedback is necessary to guide product development or application preparation. ▪ Applicable only to medical devices.
Cost	No FDA review fee	No FDA review fee
Indication Impact	Indication will drive the mechanism of action which in turn will feed into the primary mode of action.	A Pre-Sub is a submission sent to the FDA for a device or a combination product whose primary mode of action is as a device.

To be prioritized

Note: [1] Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), or Center for Devices and Radiological Health (CDRH); [2] A predicate device is a legally marketed device that does not require a Pre-Market Approval (PMA). Source: FDA website; Alira Health Analysis.

FDA Regulatory Pathways Overview (2/2)

Clinical and Regulatory Strategy

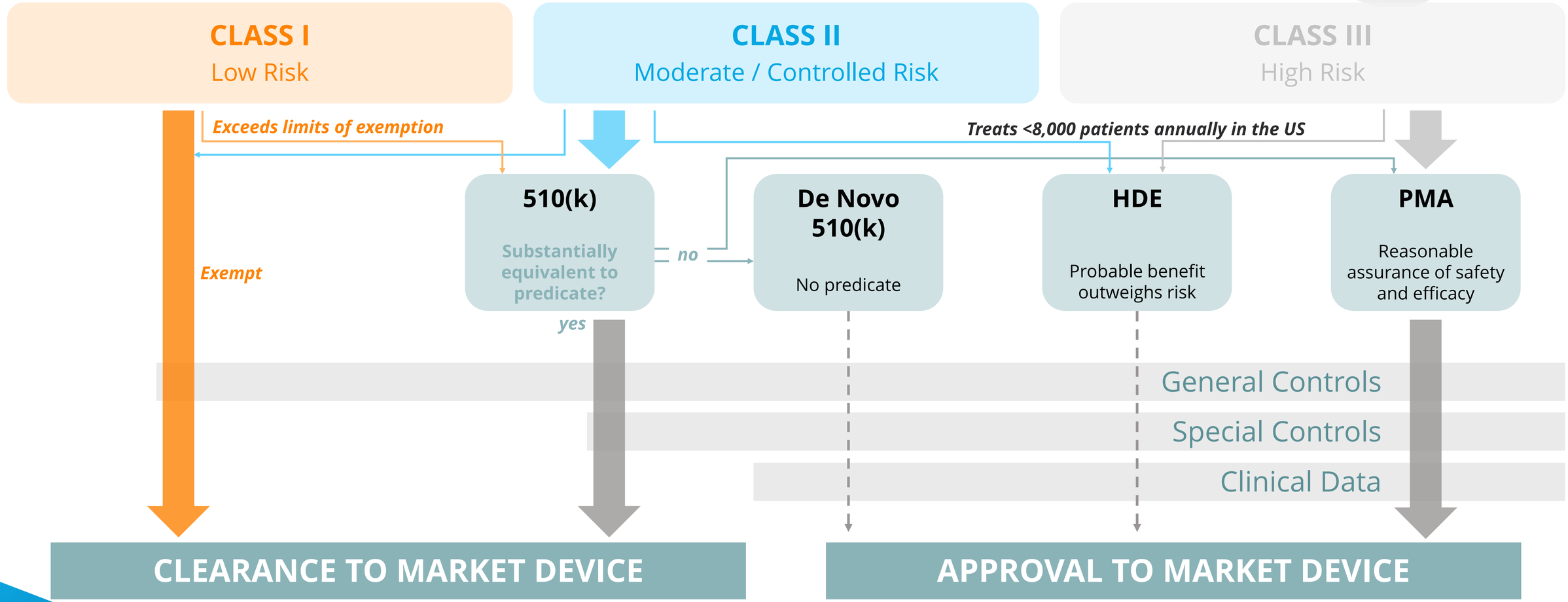
The scenario choice will determine which program should be prioritized. Imaging device software and imaging drugs (e.g. contrast agents) if commercialized together are classified as a combination product by the FDA.

	510(k)	De Novo 510(k)	Pre-Market Approval (PMA)	New Drug Application (NDA)
Product Designation	Medical Devices/Combination	Medical Devices/Combination	Medical Devices	Drug
Definition	▪ Premarket notification to notify the FDA of an intent to market a medical device. ▪ Must demonstrate that a new device is 'substantially equivalent' to a 'predicate device[2]'.	▪ This programs is suitable for devices that are low to moderate risk, for which there is no predicate may be candidates for the 510(k) de novo program. ▪ It allows the FDA to classify new types of devices into Class I or II.	▪ Process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. ▪ Class III devices are those that are implants or support or sustain human life.	▪ Vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the U.S. ▪ The data gathered during the animal studies and human clinical trials of an Investigational New Drug (IND) become part of the NDA.
Cost	$$	$$	$$$	$$$
Timeframe	6-9 months	6-12 months	1 year – 18 months	1 year – 18 months
Insights	Not a hurdle for a competitor to get a 510k for something similar	More work than a 510 (k) but much less than a PMA	Higher burden. Randomized clinical trial. Harder for a competitor to follow–Significant evidence required.	
Indication Impact	▪ Submission of a 510(k) for a new indication might be appropriate if for example the approved imaging drug and cleared imaging device are **already indicated for the same** or consistent contrast **indication**. ▪ New indications for devices using imaging drugs are likely to raise new types of safety and effectiveness questions that require review of a PMA.		▪ For changes in indications that arise from a change in the imaging device alone, that **do not affect** the imaging drug or require changes to drug labeling .	▪ Holders of a NDA or BLA for an imaging drug or biological product who seek to develop new contrast indications that refer to devices **should submit supplements to their NDA/BLA** in accordance with existing drug or biological product provisions. ▪ In addition, if the FDA approves or clears a new contrast indication in a device submission, the NDA/BLA holder may submit **a labeling supplement** to add the indication to the imaging drug.

Source: FDA website; Alira Health Analysis.

New Medical Devices Regulatory Pathways Processes

Depending on its Class, a Medical Device will have to go through different regulatory pathways whose length is difficult to estimate.



- Source: Hoffman M.J, FDA Regulatory process.

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Medical Device Regulatory Pathways Comparison

There are four main regulatory pathways for Medical Devices in the US; highly related to the devices' classes.

	Premarket Notification 510(k)	De Novo 510(k)	HDE[1]	Premarket Approval (PMA)
Definition	A 510(k) must demonstrate that the **device is substantially equivalent:** ▪ To one legally in commercial distribution in the US before May 28, 1976 ▪ Or to one that has been determined by FDA to be substantially equivalent	A De Novo addresses **novel devices** of low to moderate risk that **do not have a valid predicate device.** It can be submitted after a 510(k), or directly.	HDE are marketing application for **Humanitarian Use Device (HUD):** a medical device intended to benefit patients in the treatment or diagnosis of a rare disease / condition (affects <8,000 people/year in the US)	A PMA is used to prove that a new device is **safe and effective** for the end user
Candidates	▪ Few Class I devices ▪ Most of Class II devices ▪ Few Class III devices	▪ Few Class I devices ▪ Most of Class II devices	▪ Class I devices ▪ Class II devices	▪ Class III devices
Evidence	Comparison with predicate device	Scientific evidence	Scientific evidence	Scientific evidence
Clinical Data	Partial: 0-15% need clinical studies	Partial: 10-15% need clinical studies	Yes	Yes
Pre-Approval Inspection	No	No	No	Yes
Post-Marketing Activities	No	No	No	Yes
Advisory Panel Review	Rare	Rare	Rare	Frequent

• Note: [1]HDE: Humanitarian Device Exemption. Source: FDA.

Common Mistakes Made in the Regulatory Strategy Journey

This slide presents eight common pitfalls to avoid if one wants to have an efficient pathway to market approval. The key to overcome these barriers is to be organized and prepared; as well as communicating with the FDA.

- **Not planning** or having a regulatory strategy/pathway
- **Not submitting a Pre-Sub** to obtain FDA feedback for novel devices
- Performing **extensive testing prior to communicating** with FDA
- **Not communicating** with the FDA early in the process
- **Not understanding the history** of the device or product type in the US
- Not following or knowing **FDA guidance documents** exist
- **Not being prepared** during FDA meetings
- **Ignoring FDA feedback**

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Digital Health, Apps, SAMD and CDS

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. These include software functions that:

- Transform a mobile platform into a regulated medical device.
- Connect to an existing device type for purposes of controlling its operation, function or energy source
- Used in active patient monitoring to analyze patient-specific medical device data.

- **Software that processes uterine contraction and fetal heart rate data for remote monitoring of labor progress**
- **Software functions that use an attachment to the mobile platform to measure blood glucose levels**

Enforcement Discretion – FDA intends to exercise enforcement discretion, meaning they will not enforce requirements under the FD&C act, for some software device functions that pose a lower risk to the public**.** These functions include:

- Software functions that help patients self-manage their disease or conditions without providing specific treatment or treatment suggestions.
- Software functions that automate simple tasks for health care providers

- **Software functions that aggregate and display trends in personal health incidents**
- **Software functions that provide periodic educational information, reminders, or motivational guidance to smokers trying to quit, patients recovering from addiction, or pregnant women;**
- **Software functions that use an attachment to the mobile platform to measure blood glucose levels**

Clinical Decision Support Software

Software function is considered CDS if:

- It 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
- It is intended for purpose of displaying, analyzing, or printing medical information
- It is intended for the purpose of supporting or providing recommendations to a health care professional

- **Software that identifies patients who may exhibit signs of opioid addiction based on patient-specific data**
- **Software intended for patients that provides a questionnaire to assess a patient's level of stress and anxiety and recommends treatment options**

Non-Device CDS are CDS functions for which the HCP can independently review the basis for the recommendations provided. Non-Device CDS is not subject to FDA oversight focus.

Software that uses a patient's diagnosis to provide an HCP with current practice treatment guidelines for common illnesses or conditions

FDA Policy for CDS

Table 1. Summary of Regulatory Policy for CDS Software Functions

		Intended User is HCP		Intended User is Patient or Caregiver
IMDRF Risk Categorization	**Can the User Independently Review the Basis?**	**FDA Regulation**		**FDA Regulation**
Inform x Critical	Yes	Not a Device		Oversight Focus
	No	Oversight Focus		Oversight Focus
Inform x Serious	Yes	Not a Device		Oversight Focus
	No	Oversight Focus		Oversight Focus
Inform x Non-Serious	Yes	Not a Device		Enforcement Discretion
	No	Enforcement Discretion		Oversight Focus

Artificial Intelligence and Machine Learning

Artificial Intelligence

- defined as the science and engineering of making intelligent machines, especially intelligent computer programs
- models based on statistical analysis of data, expert systems that primarily rely on if-then statements, and machine learning.

Machine Learning

- artificial intelligence technique that can be used to design and train software algorithms to learn from and act on data.
- Some real-world examples of artificial intelligence and machine learning technologies include:
  - An imaging system that uses algorithms to give diagnostic information for skin cancer in patients.
  - A smart sensor device that estimates the probability of a heart attack.

April 2, 2019

FDA published a discussion paper "Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) - Discussion Paper and Request for Feedback"

- Describes the FDA's foundation for a potential approach to premarket review for artificial intelligence and machine learning-driven software modifications.
- IMDRF's risk categorization principles, the FDA's benefit-risk framework, risk management principles described in the software modifications guidance, and the organization-based total product lifecycle approach (also envisioned in the Digital Health Software Precertification (Pre-Cert) Program).

FDA Comments on AI Framework/Regulations

Most need premarket review

- First Step Pre-Submission
- Obtain FDA's feedback on regulatory pathway and testing plan/protocols

FDA continues to receive a high volume of marketing submissions and pre-submissions for products leveraging artificial intelligence/machine learning technologies

Increase over time

Interest in utilizing a Predetermined Change Control Plan for AI/ML-based medical products

On February 7, 2020, FDA announced its marketing authorization, through the De Novo pathway, of the first cardiac ultrasound software that uses artificial intelligence to guide users. This breakthrough device is notable not only for its pioneering intended use but also for the manufacturer's utilization of a Predetermined Change Control Plan to incorporate future modifications.

April 10, 2021-The GI Genius, developed by Cosmo Pharmaceuticals and distributed internationally by Medtronic, is designed to be compatible with all agency-approved endoscopy video systems. On the physician's feed, the add-on system highlights areas of interest, allowing for closer visual inspections, tissue biopsies or ablation, with the goal of finding cancers when they may be easier to treat.

US AI Regulatory Concerns

Clinical and Regulatory Strategy

US regulatory bodies have introduced policies to encourage innovation, however companies and entrepreneurs face major regulatory challenges, particularly around data protection and cybersecurity.

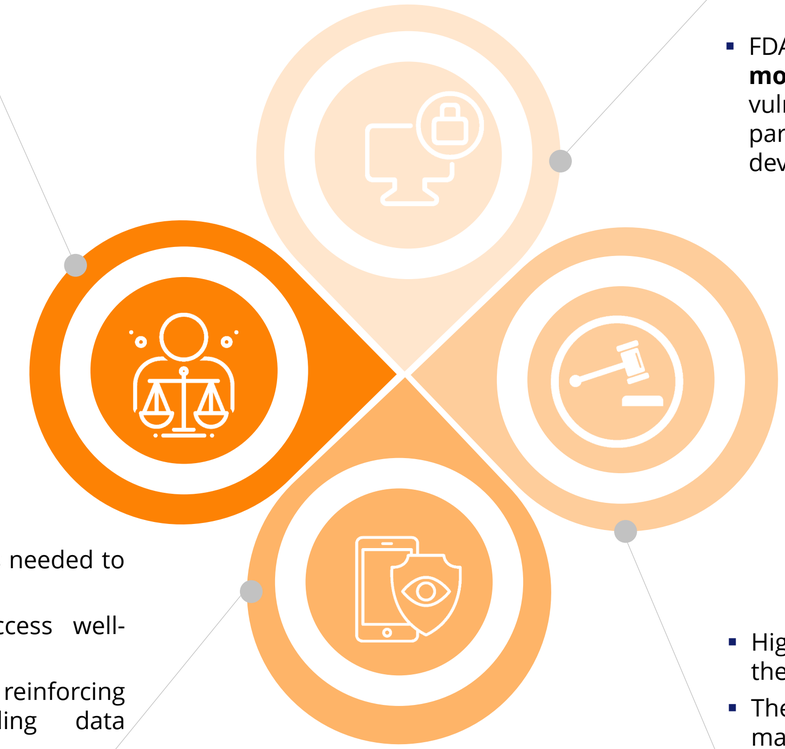
US Regulations

- US policymakers have built a **permission-less innovation** approach in which post-market data plays a major role in assessing performance. This highly promotes innovation.
- Black box nature, rapid growth of deep learning applications, and lack of definition make it **difficult for the FDA** to approve AI medical devices in a timely fashion.
- FDA clearance is harder to obtain for AI systems that do not need a **HCP supervision** and cannot be compared to **predicate medical devices.**
- Developers tend to present AI systems as **tools to aid radiologists** rather than as tools that substitute them.

Regulatory Concerns

Ethical

- Algorithms may mirror human biases in decision making.
- Healthcare delivery varies by ethnicity, adding ethical biases in the algorithm.



Cybersecurity

- FDA have emphasized that manufacturers should **monitor, identify, and address** cybersecurity vulnerabilities and areas that can be exploited, as part of their post-market management of medical devices.

Insights

FDA challenges in defining AI solution requirements and regulations induce a **high variability in the regulatory process,** especially regarding data security and inherent concerns related to responsibility and ethics.

Data Protection

- Access to big data of medical images is needed to provide training material to AI devices.
- Real competition is in place to access well-annotated big datasets.
- Illicitly harvested data has been seen reinforcing **technological regulations** regarding data protection.

Accountability and Responsibility

- High risk AI devices can be directly involved in the diagnostic and treatment decision.
- The policymakers are still questioning if the AI manufacturer or the radiologist would be responsible in case of mistakes.

Sources: Impact of AI on medical innovation in the EU and US, Tsang et.al, 2017; AI as a medical device in radiology: ethical and regulatory issues in EU and US; Pesapane et.al, 2018.

Regulatory Considerations in Covid Times…

FDA Under Health And Human Services Are Expediting The Manufacture And Approval Of Devices, Drugs And Other Technologies To Address Covid 19 Pandemic.

Getting Products to Market

2 Mechanisms

Mechanism #1

Authorizing The Use Of Devices Through Emergency Use Authorizations (EUAs)

Steps

- Submission Process
- Address Applicability
- Description, Indications
- Testing To Support Safety And Effectiveness

*

- Recinded

Mechanism #2

Exercising Enforcement Discretion Through Immediately In Effect Guidance Documents

- Comply With The Information, Testing And Labeling Described in Guidance Doc
- Those Products Can Immediately Go To Market Without FDA Intervention
  - **Ventilators** (previously cleared)
  - **Facemasks** (right to market- NIOSH)
  - **Respirators** (right to market)
  - **Disinfectants/Sterilants** (right to market
  - **Diagnostics** (EUA)
  - **Patient Monitoring** (previously cleared)
  - **Thermometers**(right to market)
  - **Infusion Pumps** (previously cleared)*
  - **PPE** (right to market –if meet standards)

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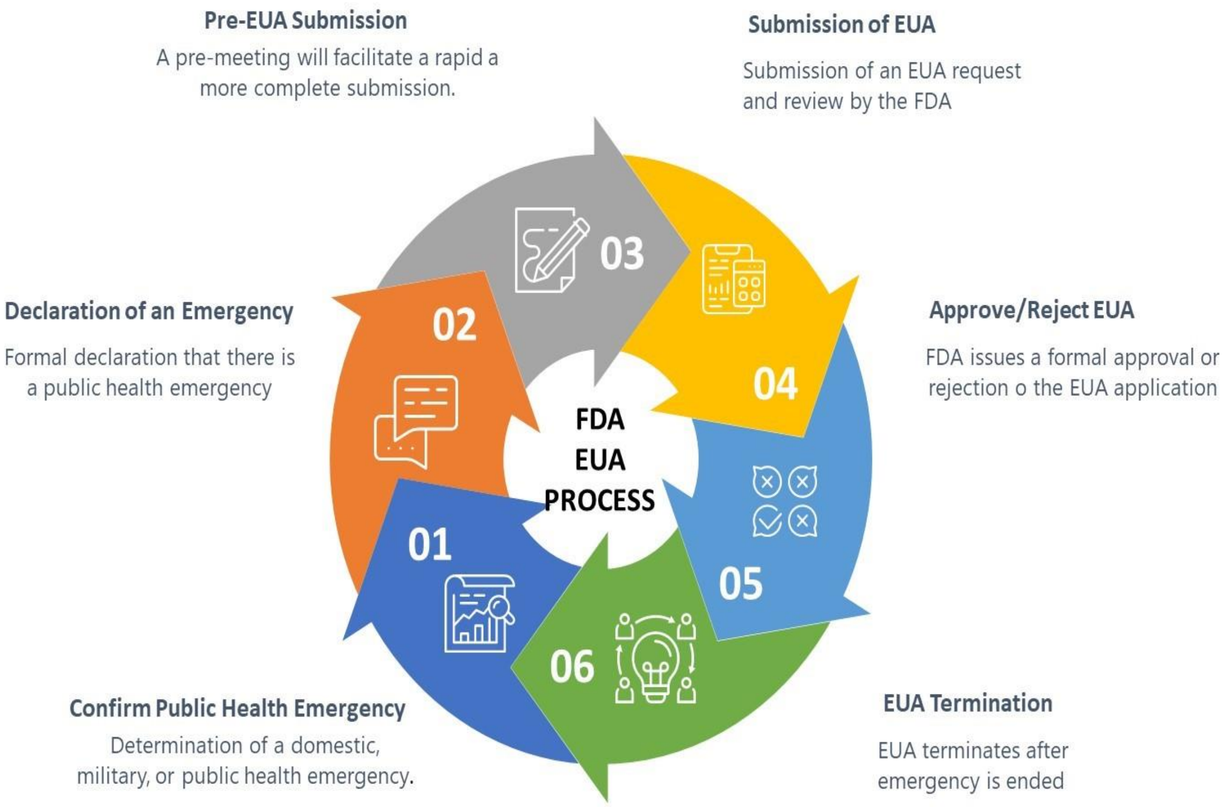
EUA Process


Pre-EUA Submission
A pre-meeting will facilitate a rapid a more complete submission.
Submission of EUA
Submission of an EUA request and review by the FDA
Declaration of an Emergency
Formal declaration that there is a public health emergency
Approve/Reject EUA
FDA issues a formal approval or rejection o the EUA application
FDA EUA PROCESS
01
02
03
04
05
06
Confirm Public Health Emergency
Determination of a domestic, military, or public health emergency.
EUA Termination
EUA terminates after emergency is ended

Highlights of FDA Activities

Ensuring Timely Availability to Accurate and Reliable Tests

Approvals

- Currently authorized 363 tests under EUAs
- 266 molecular tests,75 antibody tests and 22 antigen tests.
- 46 molecular authorizations that can be used with home-collected samples. There is one molecular prescription at-home test, one antigen prescription at-home test, and one over-the-counter (OTC) at-home antigen test
- Moderna, Pfizer and Janssen Vaccines Approved although Janssen on hold

Monitoring

- Actively Monitoring the Medical Product and Food Supply Chains to Address Imbalances
- Continue to screen and monitor millions of domestic and international products in the medical supply chain to help ensure COVID-19-related supplies coming into the U.S. are safe and distributed appropriately

Availability

- Added >90 ventilators and accessories for emergency use to ventilator EUA and issued EUAs for other equipment to treat patients
- Issued EUAs and policies to help increase availability respirators, gowns, surgical masks, etc.
- > 570 drug development programs in planning stages as of the end of July,
- Reviewed more than 270 trials of potential therapies for COVID-19

Fraudulent Activity

- FDA has identified >1068 fraudulent and unproven medical products related to COVID-19.
- FDA launched Operation Quack Hack in March 2020.
- Operation Quack Hack team has reviewed thousands of websites, social media posts, and online marketplace listings,
- Risk of False Results with the Curative SARS-Cov-2 Test for COVID-19: FDA Safety Communication

Questions/Comments……

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