Introduction to US FDA Regulatory Framework

NSF SBIR Phase I Grantee Program

Arlington, VA

September 18, 2019

Dinesh V Patwardhan Ph.D.
Agenda

- Introduction to FDA Organization
- Introduction to Centers within FDA & Combination Products
- Medical Device Amendments
- Safety and Effectiveness & Benefit-Risk Paradigm
- Quality System Regulation (QSR)
- Resources & Initiatives
  - Guidance Documents
  - Medical Device Development Tools (MDDT)
  - Digital Health Initiative
FDA touches 20-25 % of US economy
Legislative History

1902    Biologics Control Act
1906    Food & Drug Act (F&D Act)
1938    Federal, Food, Drug, and Cosmetic Act (FD&C Act)
1968    Radiation Control for Health & Safety Act (RCHSA)
1976    Medical Device Amendment of 1976
1988    Clinical Laboratory Improvement Amendments (CLIA)
1990    Safe Medical Devices Act (SMDA)
1992    Mammography Quality Standards Act (MQSA)
1992    Medical Device Amendments
1997    Food & Drug Administration Modernization Act (FDAMA)
2002    Medical Device User Fee and Modernization Act (MDUFMA)
2005    Medical Device User Fee Stabilization Act (MDUFSA)
2007    Food and Drug Administration Amendments Act of 2007 (FDAAA)
2012    FDA Safety and Innovation Act (FDASIA)
2017    FDA Reauthorization Act (FDARA) 2017
Medical Device Defined

- **Section 201(h) of the FD&C Act** defines a medical device as: (…in part…)

- A medical device is "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article

- ..intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease in man….

- ..intended to affect the structure or any function of the body,…

- and does **not** achieve its principal intended purpose by chemical action or by being metabolized.

- As low risk as a tongue depressor or a thermometer

- As complex and high risk as robotic surgery devices
• Drug

(in part)......A substance recognized by an official pharmacopoeia or formulary. A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. A substance (other than food) intended to affect the structure or any function of the body...... [FD&C Act, sec. 201(g)(1)]

• Cosmetic

(in part) ....articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body...for cleansing, beautifying, promoting attractiveness, or altering the appearance....[FD&C Act, sec. 201(i)].

• Biologic

And so on...
Combination Products Definition

• 21 CFR 3.2(e): Combination products are therapeutic and diagnostic products that combine drugs, devices, and/or biological products

• Lead center is based on “primary mode of action” (PMOA)

• Office of Combination Products
Combination Products

- Device coated or impregnated with a drug or biologic
  - Drug-eluting stent; pacing lead with steroid-coated tip; catheter with antimicrobial coating
- Examples of combination products where the components are packaged together
- Drug or biological product packaged with a delivery device
Safety & Effectiveness

• “There is reasonable assurance that a device is safe when it can be determined based on valid scientific evidence that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh the probable risks.”

• “There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.”
The mission of the Center for Devices and Radiological Health (CDRH) is to protect and promote the public health. We assure that patients and providers have timely and continued access to safe, effective, and high-quality medical devices and safe radiation-emitting products. We provide consumers, patients, their caregivers, and providers with understandable and accessible science-based information about the products we oversee. We facilitate medical device innovation by advancing regulatory science, providing industry with predictable, consistent, transparent, and efficient regulatory pathways, and assuring consumer confidence in devices marketed in the U.S.
CDRH Mission

Bring safe and effective medical devices to market as quickly as possible…

… while ensuring that medical devices currently on the market remain safe and effective.

*Provide consumers, patients, caregivers, and providers with understandable and accessible science-based information about the products we oversee.

Reference:
– CDRH Mission, Vision and Shared Values
The products we regulate…
CDRH in perspective

CDRH is a team of over 1800 employees dedicated to public health

- Engineers
- Physicians
- Biologists
- Chemists
- Physicists
- Statisticians
- Epidemiologists
- Microbiologists
- Nurses
- Veterinarians
- Toxicologists
- Public Health Education
- Communication Specialists
- Attorneys
CDRH in perspective

- CDRH oversees:
  - 175,000 medical devices on US market
  - 570,000 proprietary brands on the US market
  - 18,000 medical device manufacturers
  - 25,000 medical device facilities worldwide
  - Each year we receive
    - 22,000 premarket submissions (includes supplements and amendments)
    - 1.4 million reports on medical device adverse events and malfunctions

> 80% of device companies have <50 staff
Our job is to ensure that CDRH never has to say “I don’t know”

- Ensure readiness for emerging and innovative medical technologies
- Develop appropriate evaluation strategies and understandable public health info.
- Division of Applied Mechanics; Biology, Chemistry and Material Science; Biomedical Physics; Imaging, Diagnostics and Software Reliability.
OSEL Contributions

• Providing scientific/engineering expertise, data, and analyses

• Conducting laboratory-based regulatory research (Regulatory Science Programs)

• Facilitate Innovation & Collaboration

https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHOffices/ucm115989.htm
How to Market a Medical Device

1. Device (Product) Determination
2. Device (Product) Classification
3. Determine Appropriate Regulatory Pathway
4. Establishment Registration and Device Listing
5. Other Requirements
Product Classification Data Base
<table>
<thead>
<tr>
<th>Product Code</th>
<th>Device</th>
<th>Regulation Number</th>
<th>Device Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>KGZ</td>
<td>Accessories, Catheter</td>
<td>878.4200</td>
<td>1</td>
</tr>
<tr>
<td>KNY</td>
<td>Accessories, Catheter, G-u</td>
<td>876.5130</td>
<td>2</td>
</tr>
<tr>
<td>GCE</td>
<td>Adaptor, Catheter</td>
<td>878.4200</td>
<td>1</td>
</tr>
<tr>
<td>EYI</td>
<td>Adaptor, Ureteral Catheter</td>
<td>876.5130</td>
<td>1</td>
</tr>
<tr>
<td>QEZ</td>
<td>Aspiration Thrombectomy Catheter</td>
<td>870.5150</td>
<td>2</td>
</tr>
<tr>
<td>PTT</td>
<td>Biliary Catheter For Irrigation And Contrast Injec</td>
<td>876.5010</td>
<td>2</td>
</tr>
<tr>
<td>GCA</td>
<td>Biliary Catheter For Stone Removal That May Also A</td>
<td>876.5010</td>
<td>2</td>
</tr>
<tr>
<td>DQR</td>
<td>Cannula, Catheter</td>
<td>870.1300</td>
<td>2</td>
</tr>
<tr>
<td>LPB</td>
<td>Cardiac Ablation Percutaneous Catheter</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>OES</td>
<td>Cardiac Catheterization Kit</td>
<td>870.1200</td>
<td>2</td>
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<td>OEU</td>
<td>Cardiopulmonary Bypass Catheter Kit</td>
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<td>2</td>
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<td>OEX</td>
<td>Cardiovascular Catheter Sheath Introducer Kit</td>
<td>870.1340</td>
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<tr>
<td>KDH</td>
<td>Catheter (Gastric, Colonic, Etc.), Irrigation And</td>
<td>876.5980</td>
<td>2</td>
</tr>
<tr>
<td>JOL</td>
<td>Catheter And Tip, Suction</td>
<td>880.6740</td>
<td>2</td>
</tr>
<tr>
<td>FEZ</td>
<td>Catheter And Tube, Suprapubic</td>
<td>876.5090</td>
<td>2</td>
</tr>
</tbody>
</table>
Determination & Classification

• Cannot determine Device (Y/N)
  DeviceDetermination@fda.hhs.gov

• Cannot determine Classification

• 513 g

• Written Response
# Class of Medical Devices

<table>
<thead>
<tr>
<th>Class</th>
<th>Risk</th>
<th>Controls</th>
<th>Submission Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Lowest</td>
<td>General</td>
<td>• Exempt</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 510(k)</td>
</tr>
<tr>
<td>II</td>
<td>Moderate</td>
<td>General and Special (if available)</td>
<td>• Exempt</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 510(k)</td>
</tr>
<tr>
<td>III</td>
<td>Highest</td>
<td>General and PMA</td>
<td>• PMA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• HDE</td>
</tr>
</tbody>
</table>

References:
- [Regulatory Controls](#)
- [Class I/II Exemptions](#)
Valid Scientific Evidence

• Establish safety and effectiveness

• Progressive Evidentiary Paradigm:

  4. Clinical Data
  3. Animal (\textit{in vivo})
  2. Bench (engineering)
  1. Descriptive information (no new)
FDA Quality System Regulation (QSR)

Discovery / Ideation → Proof of Concept → Prototyping

Monitoring / Improvement ← Manufacturing / Launch ← Scale Up
Does it work?

How does it work?

How well does it work?

How well does it need to work?

How good (design) is good enough? (Risk)

…FDA QSR…
The design is good enough if . . .

regulatory and business processes are grounded in quality management, risk management, standards, and

decisions are based on legal, scientific, and engineering principles, as evidenced/supported by textbooks, professional literature, consensus standards, past experience.

Quality System (QS) Regulation/Medical Device Good Manufacturing Practices

Introduction

Manufacturers must establish and follow quality systems to help ensure that their products consistently meet applicable requirements and specifications. The quality systems for FDA-regulated products (food, drugs, biologics, and devices) are known as current good manufacturing practices (CGMP's). CGMP requirements for devices in part 820 (21 CFR part 820) were first authorized by section 520(f) of the Federal Food, Drug, and Cosmetic Act (the act). Under section 520(f) of the act, FDA issued a final rule in the
Resources & Initiatives

• Guidance Documents
• Medical Device Development Tools
• Digital Health Initiative
Guidance Documents

• In some cases intersection of Regulatory Policy and Science/Engineering

• Guidance documents represent FDA's current thinking on a given topic. They do not create or confer any rights for or on any person and do not operate to bind FDA or the public

• You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations

• Draft and Final Guidance

• Comment Period for Guidance

https://www.fda.gov/regulatory-information/search-fda-guidance-documents#guidancesearch
The table below lists all official FDA Guidance Documents and other regulatory guidance. You can search for documents using key words, and you can narrow or filter your results by product, date issued, FDA organizational unit, type of document, subject, draft or final status, and comment period.

This feature is provided to give a convenient way to search for all FDA guidance documents from a single location.

If you cannot find the document you're looking for here, you can browse separate collections of guidance documents by topic.
Medical X-ray and Imaging Devices

Pediatric Information for X-ray Imaging Device Premarket Notifications

Guidance for the Submission of 510(k)s for Solid State X-ray Imaging Devices

Medical X-Ray Imaging Devices Conformance with IEC Standards

Clarification of Radiation Control Regulations For Manufacturers of Diagnostic X-Ray Equipment: Draft Guidance for Industry and Food & Drug Administration Staff
✓ Digital Health

- Software as a Medical Device (SAMD): Clinical Evaluation - Guidance for Industry and Food and Drug Administration Staff (PDF - 1.2MB)
- Clinical and Patient Decision Support Software - Draft Guidance for Industry and Food and Drug Administration Staff (PDF - 461KB)
- Changes to Existing Medical Software Policies Resulting from Section 3060 of the 21st Century Cures Act - Draft Guidance for Industry and Food and Drug Administration Staff (PDF - 547KB)
- General Wellness: Policy for Low Risk Devices - Guidance for Industry and Food and Drug Administration Staff (PDF - 786KB)
- Mobile Medical Applications - Guidance for Industry and Food and Drug Administration Staff (PDF - 1.3MB)
Medical Device Development Tools (MDDT)

- Medical Device Development Tools (MDDT) program is a way for the FDA to qualify tools that medical device sponsors can use in the development and evaluation of medical devices

- Clinical outcome assessment
- Biomarker test
- Nonclinical assessment model
Clinical outcome assessment: measures of how a patient feels or functions. These could be patient-reported or clinician-reported rating scales like the NIH stroke scale, measures based on clinical decision-making, observer-reported outcomes such as from a parent or caregiver, or performance outcome measures, such as measures of gait speed or memory recall.
Biomarker test: a lab test or instrument used to detect or measure an indicator of biologic processes or pharmacologic responses to a treatment (biomarker). Examples of tools that might be eligible for qualification include:

- tests used as an aid in diagnosis, for patient selection, or as
- clinical study endpoints, such as instruments or methods for measuring blood pressure; or
- instruments or methods for measuring certain concentrations of serum proteins, such as an assay to detect the level of a specific hormone in a patient in order to determine enrollment eligibility for study population in a clinical trial.
Nonclinical assessment model: a nonclinical test method or model (e.g. in vitro “bench,” animal or computational model) that measures or predicts device function or performance in a living organism. Examples of tools that might be eligible for qualification include: models used to measure a parameter of interest or to substitute for another generally accepted test or measurement, such as computer modeling to assess conditions typically evaluated through human, animal or bench testing to evaluate a device instead of collecting data from human subjects; use of tissue and other material phantoms to evaluate imaging devices; or In vitro models to replace animal testing.
Qualification of Medical Device Development Tools

Guidance for Industry, Tool Developers, and Food and Drug Administration Staff

Document issued on: August 10, 2017

The draft of this guidance document was issued on November 14, 2013.

For questions regarding this document, contact MDDT@fda.hhs.gov.
Medical Device Development Tool

Qualified Tools

The FDA is excited to announce that we have qualified the first tool under the MDDT program.

The FDA will publicly list MDDTs in the table below once they are qualified, along with a summary of evidence and basis of qualification for the tool. This information includes a brief description of the tool, the qualified context of use, a general summary of evidence to support qualification, a brief assessment of the advantages and disadvantages, and information on how to contact the tool developer about accessing the tool.

<table>
<thead>
<tr>
<th>Name of Tool</th>
<th>Summary of Evidence and Basis for Qualification (SEBQ)</th>
<th>Product Area(s)</th>
<th>Tool Type</th>
<th>Date Qualified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue Mimicking Material (TMM) for Preclinical Acoustic Performance Characterization of High Intensity Therapeutic Ultrasound (HITU) Devices</td>
<td>TMM Qualification Summary</td>
<td>Imaging</td>
<td>NAM</td>
<td>7/10/2019</td>
</tr>
<tr>
<td>OSIRIX CDE Software Module</td>
<td>Qualification Summary</td>
<td>Neuro</td>
<td>BT</td>
<td>03/12/2019</td>
</tr>
<tr>
<td>Minnesota Living with Heart Failure Questionnaire (MLHFQ)</td>
<td>MLHFQ Qualification Summary</td>
<td>Cardio</td>
<td>COA</td>
<td>03/19/2018</td>
</tr>
<tr>
<td>Kansas City Cardiomyopathy Questionnaire (KCCQ)</td>
<td>KCCQ Qualification Summary</td>
<td>Cardio</td>
<td>COA</td>
<td>10/19/2017</td>
</tr>
</tbody>
</table>

The FDA will not place limitations or requirements on MDDT licensing or fees, or the degree of access to intellectual property associated with an MDDT that a tool developer may give to a device sponsor. Prior to participating in the program, the tool submitter can discuss with the FDA during the proposal phase the level of information they deem appropriate for public disclosure.
Resources & Initiatives

• Guidance Documents
• Medical Device Development Tools
• Digital Health Initiative
Digitalization Across the Health Care Continuum

Leveraging computing power, sensors, connectivity and software.

Moving health care from the Clinic to the Patient.

Understanding patient’s behavior and physiology “In the wild”.

Focusing on prevention for early/smaller interventions.
The new law amended the definition of “device” in the Food, Drug and Cosmetic Act to exclude certain software functions intended...

- for administrative support;
- for maintaining or encouraging a healthy lifestyle;
- to serve as a electronic patient records;
- for transferring, storing, converting formats, or displaying clinical laboratory test or other device data and results and certain other related information; and
- to provide recommendations to health care professionals for clinical decisions, where the user can independently review the basis of the recommendation.
Smart Regulation Principles for Digital Health Technologies

- Platform Independent
- Promote Innovation
- Promote Patient Engagement
- Protect Patient Safety

- Functionality Focused
- Narrowly Tailored

Risk Based
Facilitating Digital Health Innovation

Digital Health

Email Digital Health and 21st Century Cures Act Questions to the FDA

Read Our Digital Health Innovation Action Plan

The Digital Health Innovation Action Plan outlines our efforts to reimagine the FDA’s approach to ensuring all Americans have timely access to high-quality, safe and effective digital health products. As part of this plan, we committed to several key goals, including increasing the number and expertise of digital health staff at the FDA, launching the digital health software precertification pilot program (“Pre-Cert”) and issuing guidance to modernize our policies.

Commissioner’s Statement: Advancing new digital health policies to encourage innovation, bring efficiency and modernization to regulation

The broad scope of digital health includes categories such as mobile health (mHealth), health information technology (IT), wearable devices, telehealth and teledermatology, and personalized medicine.

Providers and other stakeholders are using digital health in their efforts to:

- Reduce inefficiencies,
- Improve access,
- Reduce costs,
- Increase quality, and,
- Make medicine more personalized for patients.
Digital Health Few Topics e.g.

1. Mobile Medical Applications (MMA)
2. Wireless Medical Devices
3. Cybersecurity
4. Software as Medical Device (SaMD)
A "Mobile Medical App" is a software application that can be executed (run) on a mobile platform (i.e. mobile app) that meets the definition of device, and is either intended to:

• be used as an accessory to a regulated medical device; or

• transform a mobile platform into a regulated medical device.
MMA Examples on our Website

- More information on MMA website:

Mobile Medical Applications

- What are mobile medical apps?
- How will the FDA regulate mobile medical apps?
- Mobile medical apps that the FDA will regulate
- Mobile apps for which the FDA intends to exercise enforcement discretion
- Does the FDA regulate mobile devices and mobile app stores?
- Mobile Medical Applications - Guidance for Industry and Food and Drug Administration Staff (PDF - 1.3 MB)
- Does the guidance apply to electronic health records?

The widespread adoption and use of mobile technologies is opening new and innovative ways to improve health and health care delivery.

Mobile applications (apps) can help people manage their own health and wellness, promote healthy living, and gain access to useful information when and where they need
Wireless Medical Devices

- Description
- Coordination with Federal Communications Commission (FCC)
- Benefits and Risks
- Information for Patients
- Information for Health Care Facilities: Risk Management
- Information for RF Wireless Developers and Manufacturers
- RF Wireless Coexistence Challenges
- Regulations
- FDA Recognized Standards Related to Wireless Medical Devices
- Industry Guidance and Guides
- Reporting Problems to FDA
Cybersecurity

Cybersecurity

Save the Date: 2019 Advisory Committee Meeting

On September 10, 2019, the Committee will discuss and make recommendations on the topic Cybersecurity in Medical Devices: Communication That Empowers Patients.

For more information, see CDRH Patient Engagement Advisory Committee.

Webcast Information: To join the webcast for the September 10 meeting of the Patient Engagement Advisory Committee, see Webcast Information.

All medical devices carry a certain amount of benefit and risk. The FDA allows devices to be marketed when there is a reasonable assurance that the benefits to patients outweigh the risks.

Medical devices are increasingly connected to the Internet, hospital networks, and other medical devices to provide features that improve health care and increase the ability of health care providers to treat patients. These same features also increase the risk of potential cybersecurity threats. Medical devices, like other computer systems, can be vulnerable to security breaches, potentially impacting the safety and effectiveness of the device.

Threats and vulnerabilities cannot be eliminated, therefore, reducing security risks is especially challenging. The health care environment is complex, and manufacturers, hospitals, and facilities must work together to manage security risks.

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- Cybersecurity Guidances
- Cybersecurity Safety Communications
- Reporting Cybersecurity Issues
- MDTs on Cybersecurity in Medical Devices
- Workshops and Webinars on Cybersecurity
- Other Collaborations on Cybersecurity
- Cybersecurity in the News
Software as a Medical Device (SaMD)

As technology continues to advance all facets of health care, software has become an important part of all products, integrated widely into digital platforms that serve both medical and non-medical purposes. Software, which on its own is a medical device — Software as a Medical Device — is one of three types of software related to medical devices. The other two types of software related to medical devices include software that is integral to a medical device (Software in a medical device) and software used in the manufacture or maintenance of a medical device.

What is Software as a Medical Device?

The term Software as a Medical Device (SaMD) is defined by the International Medical Device Regulators Forum (IMDRF) as “software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device.”

Use of Software as a Medical Device is continuing to increase. It can be used across a broad range of technology platforms, including medical device platforms, commercial “off-the-shelf” platforms, and virtual networks, to name a few. Such software was previously referred to by industry, international regulators, and healthcare providers as “standalone software,” “medical device software,” and/or “health software,” and can sometimes be confused with other types of software.

How are Regulators Addressing the Challenges with Software as a Medical Device?

Given the unique features of Software as a Medical Device that extend beyond a traditional medical device or hardware, regulators across the globe recognized the need to converge on a common framework and principles for Software as a Medical Device that enables all stakeholders, including regulators, to promote safe innovation and protect patient safety.

The International Medical Device Regulators Forum (IMDRF) is a voluntary group of medical device regulators from around the world who have come together to reach harmonization on medical device regulation. IMDRF develops internationally agreed upon documents related to a wide variety of topics affecting medical devices. In 2013, IMDRF formed the Software as a Medical Device Working Group (WG) to develop guidance supporting innovation and timely access to safe and effective Software as a Medical Device globally. Chairied by the FDA, the Software as a Medical Device WG agreed upon the key definitions for Software as a Medical Device, framework for risk categorization for Software as a Medical Device, the Quality Management System for Software as a Medical Device, and the clinical evaluation of Software as a Medical Device.
Industry Education Resources

1. CDRH Learn – Multi-Media Industry Education
   - over 80 modules
   - videos, audio recordings, power point presentations, software-based “how to” modules
   - mobile-friendly: access CDRH Learn on your portable devices

2. Device Advice – Text-Based Education
   - [https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance](https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance)
   - comprehensive regulatory information on premarket and postmarket topics

3. Division of Industry and Consumer Education (DICE)
   - Contact DICE if you have a question
   - Email: DICE@fda.hhs.gov
   - Phone: 1(800) 638-2014 (Hours: 9 am-12:30 pm; 1 pm-4:30pm EST)
   - Web: [https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice](https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice)
Thank you
dinesh.patwardhan@fda.hhs.gov