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Gaining the Edge –
Medical Device Product Development to Regulatory Compliance

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Objectives

What are Medical devices?

Regulatory Plan/Strategy – Where to Start

Device Documentation- DHF, DMR, DHR?

Product Development- Competitive Edge

US FDA- Evolving Framework

Resources, References, and Answers to Questions

This presentation will provide a general overview of the medical device landscape for a sound regulatory plan/strategy and explain how it can provide a competitive edge for product development. Additionally, the speaker will provide a list of reference material and briefly discuss the evolving framework for new devices and combination products clearance/approval by the US FDA.

FDA's Definition of A Medical Device

- Instrument
- Apparatus
- Implement
- Machine
- Contrivance
- Implant
- In vitro reagent
- or other similar or related article including a component, part, or accessory

➢ Recognized in the National Formulary or US Pharmacopoeia

➢ Intended for
  - Use in the diagnosis of disease or other conditions
  - For the cure, mitigation, treatment, or prevention of disease

➢ Intended to affect the structure or any function of the body
  - Does not achieve its primary intended purpose through chemical action within or on the body

Medical Device Classification

Devices are classified as I, II, III, or Exempt class I or II

- Class I- Low risk- general controls
- Class II- Medium risk- general + special controls
- Class III: High risk- general + special controls, sustain life/excessive risk

Significant Risk?

- Does the device have potential for serious risk to health/safety of patients/subjects?
- Does the IRB agree with the risk determination proposed?

Classification Unclear, Predicate Device Unknown, Risk Profile Questionable…now what?

- **Q Sub Meetings**
  - Discussion with FDA for guidance and informational exchange
- **Request for Designation**
  - Formal procedure for FDA feedback on classification and regulatory requirements
  - Combination products add complexity (drug/device/biologic mixed)
  - De Novo Process (risk-based classification)
- **A wavier or exemption can change the pathway for any device if justified.**
- **Getting the FDA's concurrence with your strategy early provides credibility to investors and ensures you are aligned with FDA regarding your timelines and expected outcomes.**

Q Submission Program

Q Sub Program Replaced the Pre-IDE Program established in 1995

Voluntary on the part of the submitter

Device Applicable Types include

- Pre-Submission (Pre-Sub)
- Submissions Issues Request (SIR)
- Study Risk Determination
- General Information Meetings
- Other Q Submission Types
  - Breakthrough Devices Program Submissions
  - Safer Technologies Program (“STeP”) Submissions
  - Accessory Classification Requests
  - Medical Device Development Tool Feedback Request
  - Combination product agreement meetings (CPAM)

Pre-Submissions (Pre-Sub)

- The Program is voluntary on the part of a submitter
- Formal Request for written feedback from FDA
- In-person or by teleconference as you prefer
- Opportunity to obtain FDA feedback to IDE, PMA, HDE, De Novo request, 510(k), Accessory Classification Request, etc.

Request should include;

- Specific questions regarding review issues for IDE, CW, or marketing submission-
  - questions regarding cybersecurity considerations for the device; non-clinical testing protocols; design and performance of clinical studies and acceptance criteria).

A Pre-Sub is appropriate when FDA's feedback on specific questions is necessary to guide product development and/or submission preparation.

Submissions Issues Request (SIR)

- **A SIR is a request for FDA feedback on a proposed approach to address issues conveyed in a submission**
  - PMA, HDE, De Novo request, 510(k), Dual, (or BLA) hold letter, a CW hold letter, an IDE Letter, or an IND Clinical Hold letter.
  - Types of Hold Letters applicable to Devices
    - Additional Information Needed for 510(k)s, De Novo requests, CWs, and Duals;
    - Major Deficiencies, Not Approvable, Approvable with Deficiencies, Approvable Pending GMP, and Approval with PAS conditions for PMAs and HDEs;
  - **Mechanism to quickly resolve or clarify issues**
    - not appropriate for discussing letters conveying final decisions, such as Not Substantially Equivalent, Withdrawals, and Deletions.
    - not necessary for simple requests for clarification of issues in a letter where the involvement of management is not needed

Study Risk Determination

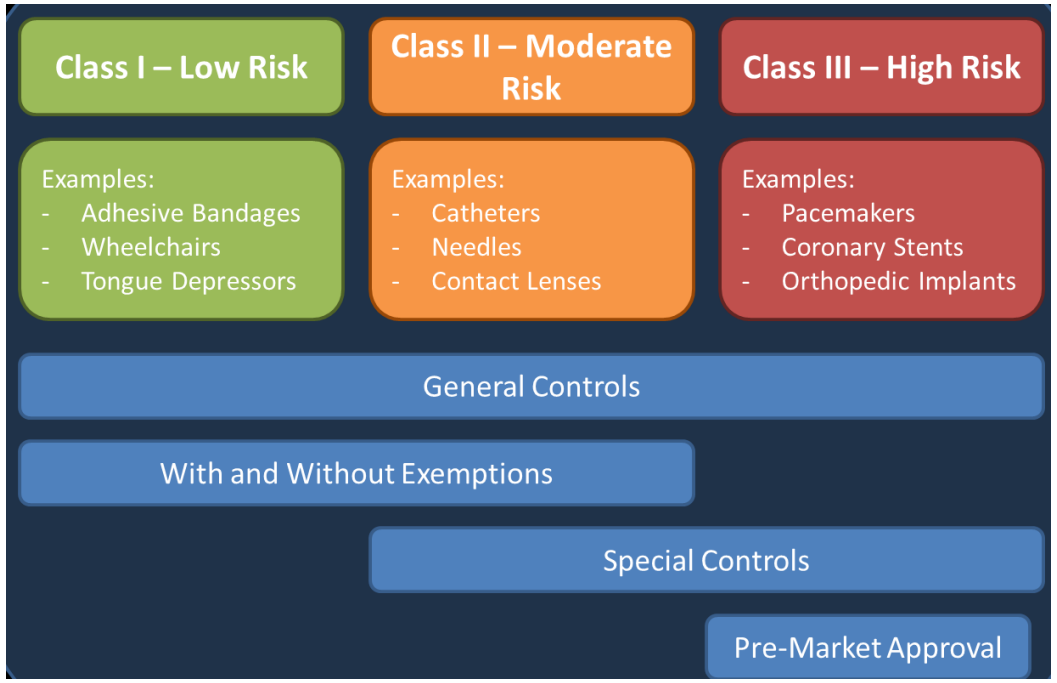
Request for FDA determination for whether a planned medical device clinical study is

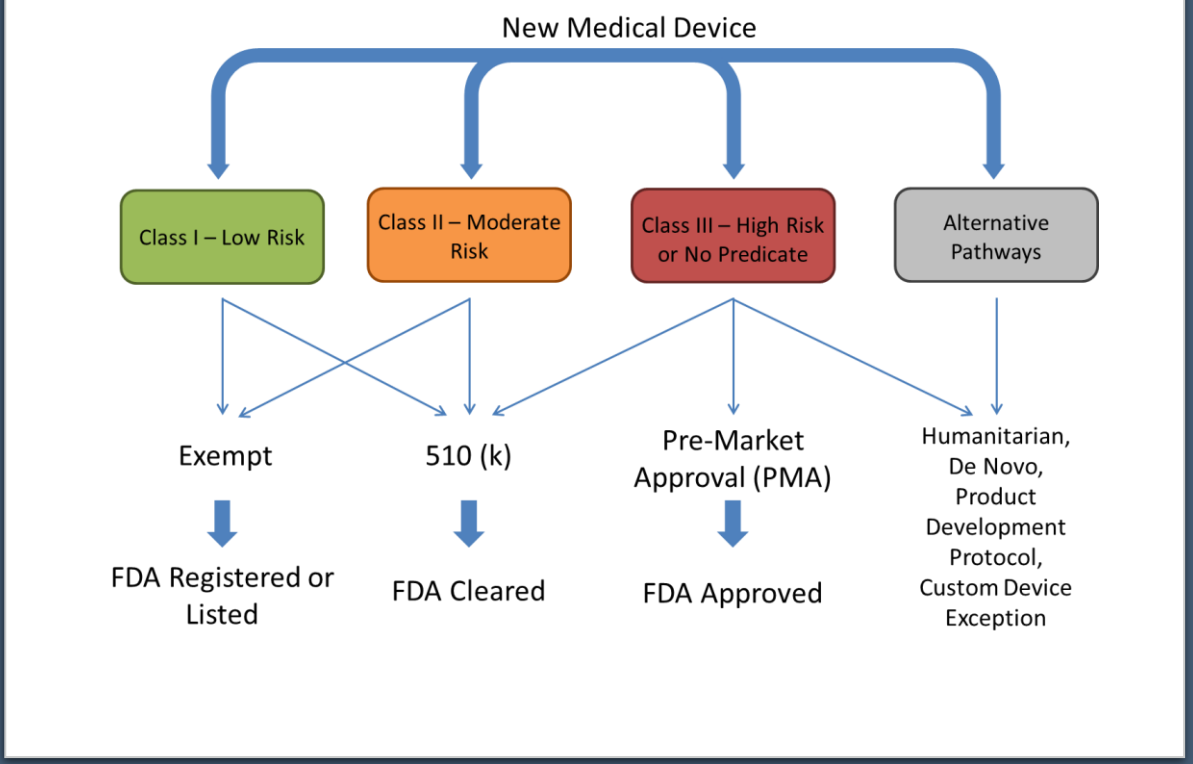
- significant risk (SR), non-significant risk (NSR), or exempt from IDE regulations as defined by the IDE regulations
- For studies that are not exempt, sponsors are responsible for making the initial risk determination (SR or NSR) and presenting it to the Institutional Review Board (IRB).
- FDA is available to help the sponsor, clinical investigator, and IRB in making the risk determination.
- FDA is the final arbiter as to whether a device study is SR or NSR
  - makes the determination when an IDE is submitted to FDA or
  - if asked by the sponsor, clinical investigator, or IRB.

General Information Meetings

- **Request to share information with FDA without the expectation of feedback**
- **For Providing an overview of ongoing device development**
  - particularly when there are multiple submissions planned within the next 6-12 months
  - familiarizing the FDA review team about new device(s) with significant differences in technology from currently available devices
- **Document FDA and submitter interactions that do not fall within the definition of the other types of Q-Submissions**

Medical Device Classifications and FDA Regulatory Pathways





Is an Investigational Device Exemption (IDE) Needed?

Purpose of an IDE

- Protection of Public Health and Safety
- Driven by Ethical Standards
- Optimum freedom for scientific investigators
- Encourage discovery/development of devices intended for Human use

Pivotal decision regarding timelines, studies, and budget

Scientific rigor of a clinical study and the robustness of evidence collected should not be based on IDE status

What is an Investigational Device Exemption (IDE)?

- **Authorization for device use in a clinical study**
  - Collect safety and effectiveness data
  - Evaluate certain modifications or new intended uses of already marketed devices

- **PMA Submissions in support of Class III device approvals**

- **Clinical evaluation of devices that have not been cleared for marketing require**
  - an institutional review board (IRB) approved investigational plan
  - informed consent from all patients
  - device labeling “For Investigational Use Only”
  - Study monitoring
  - required records and reports
  - **FDA approved IDE or waiver**

How Do I get an IDE Waiver?

IDE Waiver Criteria

- Legally marketed devices used as labeled/intended.
- Device is being used in a manner that has non-significant risk.
- Device is listed in category included on the Class I & Class II Exemption Devices List.
  - **21 CFR 862 – 892**
  - Grandfathered in from original amendment (5/28/76)

Regulatory Submission Type and Timelines

Class I

- No FDA submission is required prior to introduction into commerce
- Must develop and manufacture according to General Controls regulations
  - Quality Management System in place
  - Good Documentation practices

Class I/II Exempt

- exempt from premarket notification [510(k)] requirements as well as the Medical Device Good Manufacturing Practices (GMPs), also referred to as the Quality System (QS) Regulation.
- Must still comply with other requirements (known as regulatory controls) unless the device is explicitly exempt from those requirements as indicated in the regulation for that device type.

Regulatory Submission Type and Timelines

Class II

- Requires a **510(k) submission** with anticipated 90 day turn around for clearance of device (average is 5-6 months post submission)
- Formal process with required documentation
- General controls plus GMP

Class III

- **PMA Submission** pathway with longest timeline to approval of device (Average is 8-9 months post submission)
- Formal process with extensive clinical and testing data
- 95% confidence levels for sensitivity/specificity performance
- Highest Risk category- potential to be life threatening if fails to perform as expected

Regulatory Considerations- Gaining the Competitive Edge

Many factors impact the ability to obtain regulatory approval for a medical device

Things to consider:

- Is the product a combination product?
  - Is it a device, drug or biologic?
  - What is the primary mode of action?
- Is there another marketed device that is similar?
- Does the device address an unmet medical need in the market?
- What level of control is needed to ensure that it is safe and effective?
- How will your device be classified?

Elements of A Good Regulatory Strategy- Competitive Edge

Recommendations for Sponsors/Investigators:

- Determine device risk profile as early as possible
- Review and apply regulations and guidelines throughout the development and implementation of your clinical trial and/or data gathering
- Ensure adequate timelines for completion of IDE process prior to planned initiation of your clinical trial
- Communicate openly and frequently with FDA
- Ensure budget resources and timelines for product development cycle consistent with regulatory classification and approval process
- Your company's marketing and sales projections should be aligned with the regulatory strategy

Device Documentation

Design History File (DHF) - compilation of records which **describes the design history** of a finished device.

- Everything you did to make the device

Device Master Record (DMR) - compilation of records containing **the procedures and specifications** for a finished device.

- Everything you need to know to build and test the device
  - Device Specifications
  - Production Processes
  - Quality Assurance Procedures
  - Packaging and Labeling Specifications
  - Installation, Maintenance, and servicing

Device History Record (DHR) - compilation of records containing **the production history** of a finished device.

- Everything you did through the design and development process for your medical device is documented here.

Device Documentation

Design vs. Device

- The *design* history file contains the history of the design in accordance with FDA regulations.
- The *device* master record contains the documentation to build, test, package, and service the device.
- The *device* history record records the making of each lot, batch, or unit and contains or references the location of
  - *Manufacturing dates*
  - *Quantities manufactured and distributed*
  - *Acceptance records in accordance with the DMR*
  - *Primary identification label and labeling used for each batch, lot, or unit*
  - *Device Identifiers*
    - *Control numbers,*
    - *Unique device identifier (UDI)*
    - *universal product code (UPC)*

Changes to the Framework for New Devices & Combination Products

Reasons for Change

- FDA has seen continuous significant increases in these products
- Historical lines of separation in FDA medical product centers responsible for approvals/clearances are being challenged
- Introduction of Combination Products Policy Council

Business Impact Predictions:

- Combination Products 101: A Primer for Medical Device Makers by Dr. Michael Drues (2014)
  - 1/3 of all medical products under development were combination products in 2014
  - Drug-device combination products segment would grow to $115B by 2019
- Gran View Research:
  - Drug device market will be worth $177B by 2024
- Medical device outlook for 2021 and beyond By Wolters Kluwer (12/6/2019)
  - The global medical devices market in 2020 was valued at $456.9B, which is an increase at a compounded annual growth rate (CAGR) of 4.4% since 2015.

Changes to the Framework for New Devices & Combination Products

- FDA.gov website ‘refresh”
- Philosophical fostering of Drug Competition
- Cybersecurity
- Mobile medical applications
- Wireless medical devices
- Software as a Medical Device (SaMD)
- Impact of Artificial Intelligence
- Combating the Opioid Crisis
- Implementing the Office of Product Evaluation and Quality (OPEQ)
- Covid Crisis
  - driving excessive Emergency Use Authorization (EUAs) issuance in rapid time
  - Routine work on hold or significantly delayed

Changes to the Framework for New Devices & Combination Products

- Biologics with Devices
  - CBER leads and device group advises
- Drug and Devices
  - CDER leads and device group advises
- Devices and In Vitro Diagnostics (IVDs)
  - CDRH alone

FDA Is now taking a risk-based approach to the lead role

- **What is the critical element?**

Changing Environment Ahead!

Center for Device & Radiological Health (CDRH)

- Over 30 years CDRH has issued more than 450 Guidance Documents
- Staged review of those < 10 years old underway
  - FY19 – 2025
- Currently re-evaluating Device Classifications
  - Class II to Class I
  - Class I/II exempt
  - Class III to Class II
  - Age of device classification and impact of new technologies

Changing Environment Ahead!

- **Submissions and different communication structure in play with structured complex timelines**
- **Seeking industry input and taking a risk-based approach**
- **Harmonizing Medical Device Regulations with ISO Requirements**
  - 21CFR 820s
  - ISO 13485
  - **Impact of Unique Device Identification System (UDI) continues to grow**
    - AssessGUDID Database
    - Use of Symbols
    - FDA Accreditation issuing agencies

Remember……

Failure to ensure the data and documentation you gather, produce, or reference in accordance with the requirements can result in FDA's refusal to accept the information and therefore delay/prevent product clearance/approval.

FDA Regulations Applicable to Medical Devices

- Codified in the “Code of Federal Regulations”
  - 21 CFR Part 807, Establishment Registration and Device listing for Manufacturers and Initial Importers of Devices.
  - 21 CFR Part 812, Investigational Device Exemptions.
  - 21 CFR Part 814, Pre-market Approval for Medical Devices.
  - 21 CFR Part 820, Quality System Regulations.
- Applicable to clinical research in which devices are used
  - 21 CFR Part 50, Protection of Human Subjects.
  - 21 CFR Part 54, Financial Disclosure of Clinical Investigators.
  - 21 CFR Part 56, Institutional Review Board.
  - 21 CFR Part 58, Good Laboratory Practice For Nonclinical Laboratory Studies.
  - 45 CFR Part 46, Protection of Human Subjects.
- Statutory regulations for what studies require an IDE
  - http://www.fda.gov/MedicalDevices/default.htm

Reference Material and Resources

- https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/overview-device-regulation
- https://ec.europa.eu/health/md_sector/overview_en
- https://www.fda.gov/medical-devices/cdrh-international-programs/international-medical-device-regulators-forum-imdrf
- https://www.bfarm.de/EN/Home/home_node.html
- https://www.gov.uk/guidance/register-medical-devices-to-place-on-the-market
- https://accessgudid.nlm.nih.gov/
- https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices.html
- https://www.tga.gov.au/publication/australian-regulatory-guidelines-medical-devices-argmd
- https://www.fda.gov/medical-devices/guidance-documents-medical-devices-and-radiation-emitting-products/recent-final-medical-device-guidance-documents
- https://www.who.int/medical_devices/publications/en/MD_Regulations.pdf
- https://www.ich.org/

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Q&A

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