



# FDA Regulatory Process

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# How does FDA evaluate medical devices?

## Benefits & Risks

# FDA Benefit-Risk Considerations

## Assessment of Benefits:

- Type
- Magnitude and duration
- Probability of patient experiencing benefit

## Assessment of Risks:

- Severity, type, number and rates of harmful events
- Probability of harmful event
- Duration of harmful event

## Additional Factors:

- Type of submission: IDE, 510(k), HDE, PMA
- Type of study: EFS/FIH, feasibility, pivotal
- Uncertainty
- Characterization of Disease
- Patient tolerance for risk
- Availability of alternative treatments
- Risk Mitigation
- Novel technology addressing unmet need

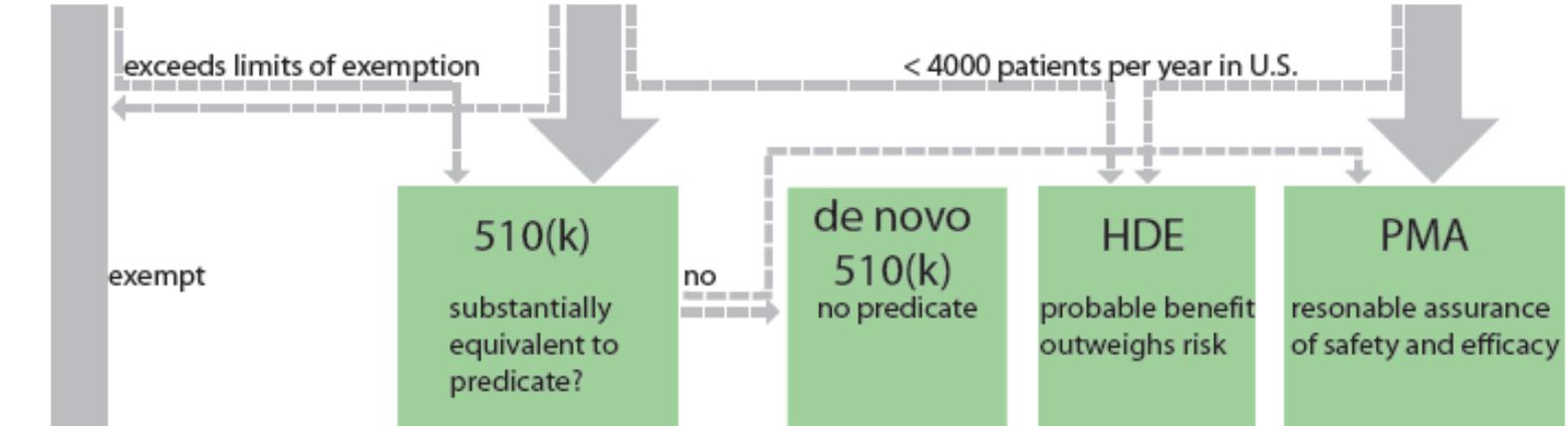
A

# NEW MEDICAL DEVICE

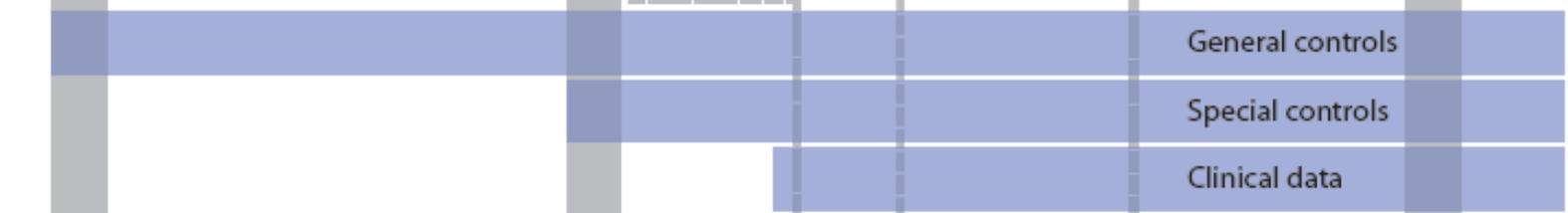
B



C



D



E





# Investigational Device Exemptions (IDEs)

# Significant & Non-Significant Risk

- **SR study:** Presents a **potential serious risk** to the health, safety, and welfare of a subject and is:
  - » an implant; or
  - » used in supporting or sustaining human life; or
  - » of substantial importance in diagnosing, curing, mitigating, or treating disease or preventing impairment of human health
  - » otherwise presents a potential for serious risk to health, safety, or welfare of a subject
- **NSR study** is one that does not meet the definition for an SR device

[21 CFR Part 812]

# Basic IDE Submission Elements

- Cover Letter
- Report of Prior Investigations
  - » prior clinical, animal, and laboratory testing of the device
- Detailed Device Description
- Investigational Plan
  - » Purpose (Proposed Indications for Use and objectives)
  - » Protocol
  - » Risk Analysis (description and analysis of all increased risks and how these risks will be minimized)
  - » Monitoring Procedures

# Basic IDE Submission Elements

- Informed Consent
- Investigator Agreement & List of Investigators
  - » Certification that all investigators have signed the agreement, that the list of investigators includes all investigators participating in the study, and that new investigators will sign the agreement before being added to the study
- List of IRBs that have or will be asked to review the investigation
- Copies of all labeling for the device

# FDA Decisions on IDEs

- **Approval**

- » Approves the trial for a specified number of patients and investigational centers
- » Subjects not exposed to unacceptable risks, even if study is not adequately designed to demonstrate the device is safe and effective

- **Conditional Approval**

- » Trial may begin if conditions (deficiencies) are addressed within 45 days.
- » Generally due to non-clinical testing issues, minor issues w/ informed consent, other clarifications, corrections, or modifications

# FDA Decisions on IDEs

- **Disapproval**

**The risks to the subjects are not outweighed by the anticipated benefits to the subjects and the importance of the knowledge to be gained, the investigation is scientifically unsound, or there is reason to believe that the device as used is ineffective**

- » Trial may not start until deficiencies are adequately addressed
- » Primarily related to subject protection (e.g., critical preclinical testing and study design concerns related to subject safety)

# FDA Additional Comments on IDEs

- **Study Design Considerations**

- » Additional modifications that FDA believes are needed in order for the study design to support a marketing approval or clearance (Pivotal Trial) or a future study (Feasibility Study)
- » Recommended (not required) modifications to the investigational plan

- **Future Considerations**

Additional considerations which FDA considers important for the support of a future submission, e.g., non-clinical testing not required for IDE but at the time of marketing application

# IDE Study Types

- **Early Feasibility Study (EFS):**
  - » a limited clinical investigation (<15)
  - » early in development, typically before the device design has been finalized, for a specific indication (e.g., innovative device for a new or established intended use, marketed device for a novel clinical application)
  - » intended to provide proof of principle and initial clinical safety data
- **First in Human (FIH) Study:** a device for a specific indication is evaluated for the first time in human subjects.

A FIH can be a EFS, but not all FIH studies would be considered EFSs.

## IDE Study Types (cont.)

- **Traditional Feasibility Study:**
  - » to capture preliminary safety and effectiveness information on a near-final or final device design
  - » to adequately plan an appropriate pivotal study.
  - » does not necessarily need to be preceded by an early feasibility study
- **Pivotal Study:**
  - » to collect definitive evidence of the safety and effectiveness of a device for a specified intended use, typically in a statistically justified number of subjects.
  - » may or may not be preceded by an early and/or a traditional feasibility study.



# **Early Feasibility Studies**

# Early Feasibility Study (EFS)

Guidance for Industry and FDA Staff:

**“Investigational Device Exemptions (IDE) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies”**

Intended to facilitate the clinical evaluation of medical devices in the US under the Investigational Device Exemptions (IDE) regulations, using risk mitigation strategies that appropriately protect study subjects

# Key Principles of an EFS

- May be appropriate when:
  - » Nonclinical testing methods are not available or adequate to provide the information needed to advance the developmental process; and
  - » Clinical experience is necessary (small # of subjects)
- The **core principle** is the application of **benefit/risk principles** throughout regulatory decision-making (keep clinical context in the forefront)
- Thorough risk analysis and mitigation strategies
- Approval may be based on less nonclinical data than would be expected for a traditional feasibility or a pivotal study.
- Strengthened Informed Consent

# EFS Highlights

## Approval Based on Less Non-clinical Data

- For some new devices, exhaustive nonclinical testing would not likely provide the information needed to further device development
- May be acceptable to complete additional tests concurrently with the EFS
- Need information to:
  - » Support an expectation of acceptable clinical use and that the device will function as intended, e.g., successful device placement using a bench-top model that simulates clinical conditions and/or a suitable animal model
  - » Address basic device safety, including, but not limited to, sterility, biocompatibility, chemical compatibility (e.g., with concomitant drugs, chemicals, cleaners)
  - » Characterize catastrophic failure modes and risk mitigation approaches



# Study Considerations for Different Development Stages

# Different Stages of Development

- Supporting evidence may vary for different stages of development
- EFS→Feasibility→Pivotal→PMKT
- Subject safety critical at each level
- Increasing emphasis placed on collecting effectiveness data and completion of additional testing (e.g. bench) needed to premarket submission

# EFS

- Sample size generally 10 but up to 15
- Bench testing:
  - » completed biocompatibility & sterility testing
  - » additional bench testing protocols complete with P/F criteria; completion of these tests at time of IDE may be subject to patient risk of associated failure
    - EMC, Electrical Safety, Mechanical, Durability, Wireless, etc.

# EFS

- Animal testing: support preliminary safety
  - » Implant location
  - » Implant duration
  - » Stimulation and recording capabilities
  - » Support premise of proposed clinical testing
  - » Study may be ongoing at time of IDE
  - » May not be necessary if animal model N/A **or** testing will not provide additional preliminary safety information (e.g., EFS)

# EFS

- Clinical testing considerations:
  - » focus on collecting safety data
  - » effectiveness endpoints exploratory to help determine appropriateness for future study
- Device modifications: expected
  - » Hardware and software modifications
  - » Algorithm optimization
  - » Materials modifications

# Traditional Feasibility Study

- Sample size typically 20 to 30
- Bench testing:
  - » complete to assure safety of subjects.
  - » Risks associated with device hazards may determine if outstanding issues result in deficiencies or future considerations
- Animal testing: additional testing may not be needed **IF** previous animal/clinical data from pilot/EF study support proposed use

# Traditional Feasibility Study

- Clinical testing considerations:
  - » clinically relevant endpoints
  - » focus on continuing safety data collection
  - » Formal effectiveness endpoints based on previous testing to inform future pivotal testing
- Device modifications: allowed
  - » consideration should be made regarding how device changes affects applicability of results across different versions of the device

# Pivotal Study

- Statistically driven sample size
- Bench testing: complete
  - » Some minor testing/retesting may still be in process depending on risks to subjects
- Animal testing: additional testing likely not needed if data from previous studies support proposed use

# Pivotal Study

- Clinical testing considerations:
  - » Clinically relevant endpoints
    - Based on proposed population and device use
    - Supported by results of previous studies
  - » Study population should reflect proposed indicated population of future marketing submission
- Device modifications: possible
  - » justification to support data applicability



# Master Files

## Master Files (MAF)

- Reference files from third party
  - » Allows third party to submit confidential information on their process, testing, component without disclosing information to Applicant of premarket submission.
- Applicant of IDE, PMA, 510(k) obtains Letter of Authorization for FDA to refer to MAF for specific part of review (materials, component, etc).

# Master files

- Examples
  - » Several applications may be submitted for different products which may use a common material or process or component.
  - » Allows multiple investigators to study same unmarketed device clinically without necessarily reperforming bench and animal tests (e.g., bench, biocompatibility).



# Pre-Submissions

# Pre-Submissions

## An opportunity to obtain FDA feedback prior to IDE or marketing submission (multiple types)

- Informational Meetings -
  - » Overview of ongoing device development when multiple submissions planned over next 6-12 months
  - » Familiarize review team about new device(s) with significant differences in technology
- Guidance on **specific issues** related to -
  - » Nonclinical and/or animal studies prior to initiation
  - » Clinical studies requiring IDE or for NSR & OUS studies

# Pre-Submissions

- Before submitting a marketing application -
  - » Obtain insight into potential hurdles (e.g., numerous protocol deviations, missing data, failed testing, etc.)
  - » Obtain feedback on preferred data presentation and required elements
  - » Apprise FDA on the particulars of the device and clinical study (if there have been changes since initiation of IDE)

# Pre-Submissions

## Key information to include:

- Cover letter
- Table of Contents
- Device Description
- Proposed Intended Use
- Reference previous discussions or submissions with FDA
- Overview of Product Development (outline of clinical & nonclinical testing already completed and planned)
- **Specific Questions**
- Mechanism for Feedback

# Pre-Submissions

## FDA Feedback:

- Goal: feedback within 75-90 days of submission receipt
- In-person meeting, teleconference, written or email response
- Represents FDA's best advice based on information known at that time point
- Modifications to feedback limited to situations in which FDA concludes that the feedback given previously does not adequately address important new issues materially relevant to a determination of safety or effectiveness that have emerged since the time of the Pre-Sub

# References & Useful Information

Early Feasibility Study/First in Human Guidance

<http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279103.pdf>

FDA Decisions for IDE Clinical Investigations Guidance

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM279107.pdf>

Presubmission Guidance

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf>

Master File Information

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm142714.htm>