IDE Basics

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Learning Objectives

- To understand the regulatory context of device clinical investigations
- To understand when an IDE is required
- To understand the IDE application process and FDA decisions on those applications
- To understand the roles of key players in IDE studies

Overview

- **Regulatory authority and framework for device clinical investigations**
- Discussion of studies requiring an IDE
- The IDE application and FDA decisions
- Office-level review of IDE application-specific issues
- Roles of sponsors, investigators, and IRBs

Section 520(g) of the FD&C Act

Exemption for Devices for Investigational Use

"It is the purpose of this subsection to encourage, to the extent consistent with the ***protection of the public health and safety*** *and with ethical standards, the* ***discovery and development of useful devices*** *intended for human use and to that end to maintain optimum freedom for scientific investigators in their pursuit of that purpose."*

Law (FD&C Act) ⇒ Regulation

Several parts of the Code of Federal Regulations (CFR) pertain to IDEs:

- 21 CFR 812 Investigational Device Exemptions
- 21 CFR 50 Protection for Human Subjects, Informed Consent (IC) Regulation
- 21 CFR 54 Financial Disclosure of Investigators
- 21 CFR 56 Institutional Review Boards (IRBs)

As of July 9, 2012 - Section 601 of FDASIA - FDA Safety and Innovation Act

Investigational Device Exemption

- 21 CFR 812.1:

  *"An approved **investigational device exemption (IDE)** permits a device that otherwise would be required to comply with a performance standard or to have premarket approval to be **shipped lawfully** for the purpose of **conducting investigations** of that device."*

- An IDE is a **regulatory submission** that permits clinical investigation of devices.

Approved IDEs are Exempt from Regulations Pertaining to:

- Misbranding
- Registration
- Performance Standards
- 510(k)
- PMA
- HDE
- Good Manufacturing Practices (GMPs) except Design Controls
- Color Additive requirements
- Banned Devices
- Restricted Device requirements

Provisions of the IDE Regulation

- Describes **applicability** of the IDE regulations
- Provides **administrative** information
- Outlines the contents of the **IDE application**
- Describes **FDA actions** on IDE applications
- Assigns **responsibilities** to participants

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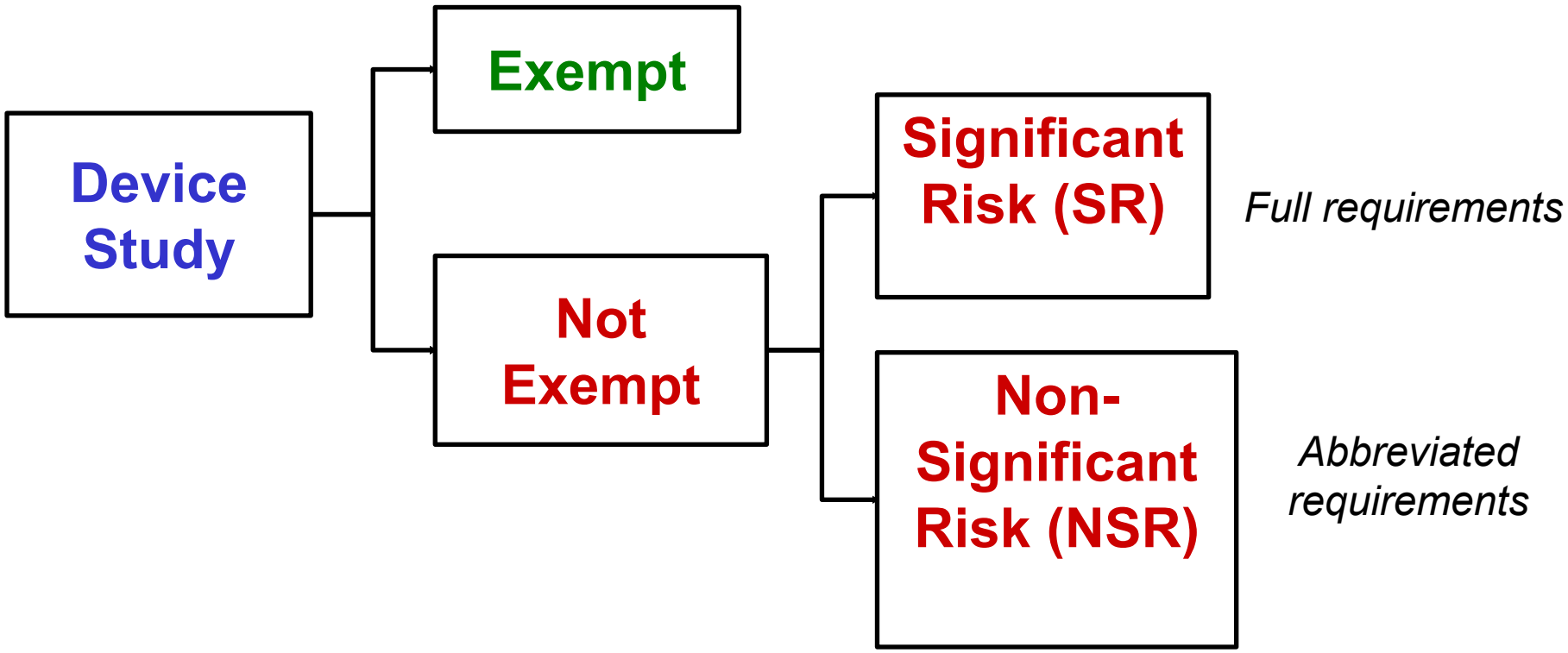
Types of Studies

- Pivotal Study
  - Designed to collect definitive evidence on safety and effectiveness for a specified intended use, typically in a statistically justified number of subjects
- Feasibility Study
  - Capture preliminary safety and effectiveness data typically in a small number of subjects (typically to inform pivotal study)
- Sponsor-investigator Studies
  - Not intended to support a marketing application

Types of Studies

- Early Feasibility Study
  - Small number of subjects
  - Device may be early in development, before final device design
  - Approval may be based on less nonclinical data than would be needed to support the initiation of a larger clinical study on a more final device design
  - Guidance ***"Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies"***

When is an IDE needed?



Exempt Studies (21 CFR 812.2(c))

No IDE Needed

- Commercial devices used in accordance with labeling
- Many diagnostic devices
- Testing of consumer preference, of a modification, or of a combination of devices, when not determining safety or effectiveness and not putting subjects at risk
- Veterinary devices or research on/with laboratory animals
- Custom devices as defined in 812.3(b)

"Practice of Medicine"

"Nothing in this Act shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship…."

From Section 1006 of the FD&C Act

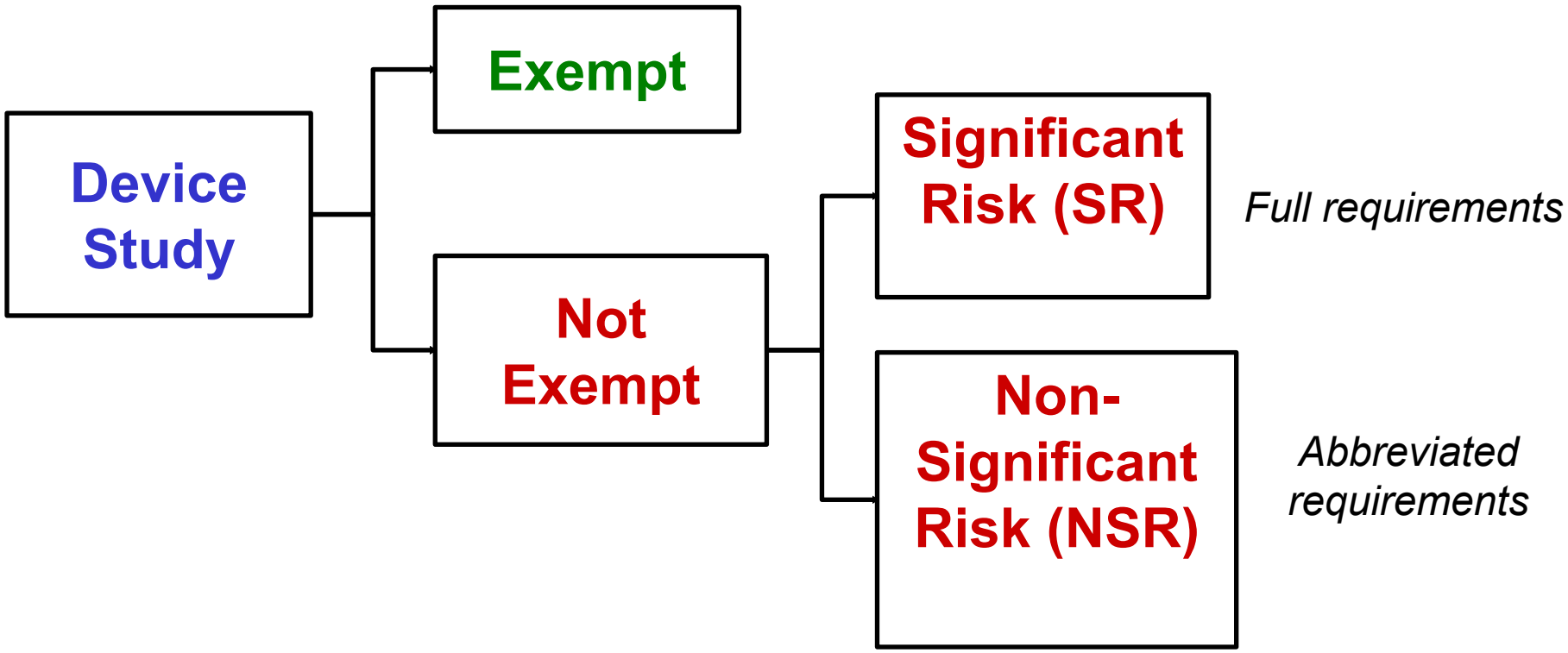
"Practice of Medicine"

- Physician should:
  - Be well informed about the product
  - Use firm scientific rationale and sound medical evidence
  - Maintain records on use and effects
- **IDE not required**; institution may require IRB review/approval and informed consent
- Other prohibitions still apply

"Basic Physiological Research"

- Investigating a physiological principle
- No intent to develop the device for marketing
- Only using the device to address the research question
- **No IDE needed;** IRB approval and informed consent should be obtained

When is an IDE needed?



Significant Risk (SR) Study

- Presents a **potential for 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 poses a risk

See 21 CFR 812.3(m)

Risk Determination

- **Sponsor** makes initial determination
- **IRB reviews** the sponsor's determination
  - Information provided by the sponsor includes device description, prior investigations, investigational plan, subject selection, risk assessment and rationale used in making its SR or NSR determination
- If the IRB disagrees with a sponsor's NSR assessment, the IRB must inform the clinical investigator, and where appropriate, the sponsor. (21 CFR 812.66)

Non-Exempt Studies

- **Non-Significant Risk** – no IDE submission to FDA needed
  - abbreviated requirements (labeling, IRB, consent, monitoring, reporting, prohibition on promotion)
  - IRB serves as the FDA's surrogate for review, approval, and continuing review of the NSR device studies.
  - An NSR device study may start at the institution as soon as the IRB reviews and approves the study
- **Significant Risk** – Study can not begin until IDE is approved by FDA

Study Risk Determination Inquiries to FDA

- FDA is available to help in making the risk determination
- Sponsor submits **"Study Risk Determination" Q-Submission**
- FDA issues letter indicating if study is
  - Basic physiological research
  - Exempt
  - Not exempt: SR or NSR
- FDA is final arbiter

"The Pre-submission Program and Meetings with FDA Staff"

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

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The IDE Application (812.20)

- Name and address of sponsor
- Report of prior investigations and investigational plan
- Manufacturing, processing, packing, and storage of device
- Investigator agreement
- List of the name, address, and chairperson of each IRB
- Participating institutions
- Charge for device
- Environmental assessment
- Labeling
- Subject materials including informed consent
- Additional information requested by FDA

FDA Review of the Application

- FDA sends acknowledgement with IDE number: GYYxxxxx (e.g. G140001)
- IDE sent to appropriate review division based on intended use
- Lead reviewer assembles team of experts to review the application and make decision with management concurrence within 30 days
- FDA issues a decision letter to the sponsor

FDA Submissions after Approval

- **Supplements** (812.35)
  - Change in protocol
  - Change in device
- **Reports** (812.150)
  - Annual progress
  - Unanticipated adverse device effects
  - Follow-up completion
  - Current list of investigators
  - Final report

FDA Decisions and Letters

- **Approval**
  - Approves the trial for specified number of sites and subjects
  - Enrollment can begin once IRB approval is obtained
- **Approval with conditions**
  - Approves the trial for specified number of sites and subjects provided conditions (deficiencies) are addressed within 45 days
  - Enrollment can begin once IRB approval is obtained
- **Disapproval**
  - Study may not begin; sponsor must address deficiencies and obtain FDA approval to start study

Regulatory Basis for Disapproval

- There has been a failure to comply with regulatory requirements
- The application contains an untrue statement of material fact, or omits material information
- The sponsor fails to respond to a request for additional information
- There is reason to believe that the
  - risks are not outweighed by the anticipated benefits to the subjects and the knowledge to be gained,
  - informed consent is inadequate,
  - investigation is scientifically unsound, or
  - device as used is ineffective

Regulatory Basis for Disapproval

- It is otherwise unreasonable to begin due to the way the device is used or the inadequacy of:
  - the report of prior investigations or the investigational plan;
  - the manufacturing, processing, packaging, storage, and/or installation of the device; or
  - monitoring and review of the investigation.

Revision to FD&C Act, July 2012

FDA shall not disapprove an IDE because:

- *The investigation may not support a substantial equivalence or de novo classification determination or approval of a device*
- *The investigation may not meet a requirement, including a data requirement, relating to the approval or clearance of a device; or an additional or different investigation may be necessary to support clearance or approval of the device*

Revision to FD&C Act

- This means that an IDE cannot be disapproved on the basis of FDA's belief that the study design is inadequate to support a future PMA, 510(k), humanitarian device exemption (HDE), or de novo classification.
  - Disapproval is based on concerns related to subject safety and protections

Other Elements of FDA Decision Letters

- **Study design considerations**
  - Recommendations (but not requirements) regarding study design to help study achieve its goals
- **Future considerations**
  - Issues relevant for future submissions (e.g. future marketing application)
- Sponsors are not required to respond to these elements

Summary: FDA Letter

- Decisions: can you start the study?
  - ☑ Approval
  - ☑ Approval with conditions
  - ☒ Disapproval

Require *deficiencies* to be addressed

- Study design considerations and future considerations do NOT require a response. They have no bearing on the IDE decision.
- Guidance: *"FDA Decisions for IDE Clinical Investigations"*
  http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279107.pdf

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SOP for Review of IDE Application-Specific Issues

- Goal of CDRH Clinical Trials Enterprise: To conduct device trials in the U.S. in a timely, efficient, and cost-effective manner, while maintaining appropriate patient protections
- Standard Operating Procedure (SOP) in place to improve efficiency, consistency, and predictability of the IDE process
- http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm384135.htm

SOP Policy and Scope

- IDE approvability decisions typically made at Division level.
- With SOP, Office-level Clinical Trials Director (CTD) is involved in selected submissions
  - Provides objective review of outstanding issues to help resolve specific challenges
- Applies to original IDEs, new study supplements, and expansions of studies from feasibility to pivotal for which a decision other than full approval is made

SOP Provisions

- Teleconference with sponsors
  - FDA offers a teleconference to occur within 10 days of a 1st round disapproval (DSAP) or 2nd (or later) round DSAP or approval with conditions (APCN)
- CTD review of DSAP and APCN decisions
  - CTD and review team meet prior to 10-day t-con to discuss IDE and remaining issues
- CTD interaction *during review* of 3rd (and subsequent) round response to DSAP or APCN

SOP Goals

- To help ensure consistency in decision-making
- To facilitate sharing of best practices across divisions
- To encourage higher levels of interaction
- To help prepare sponsor to respond
  - 10-day meeting
  - “Outside” perspective on letter

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Key Players

- **Sponsor:** initiates, but does not actually conduct, the investigation
- **Investigator:** actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject
- **Institutional Review Board (IRB):** reviews, approves (initially and continuing) biomedical research at a given institution

Sponsor Responsibilities

- Select qualified **investigators** and provide them with information they need
  - Obtain investigator agreements
- Ensure proper **monitoring**
  - Select appropriate monitors
  - Secure compliance, evaluate and handle unanticipated adverse device effects
- Obtain **IRB and FDA** review and approval
  - For study initiation and for resumption of terminated studies
  - IDE application and supplements
  - Keep IRB and FDA informed of significant new information
- Control **devices**
- **Comply** with Subpart A (labeling, promotion, import/export)

Sponsor Responsibilities Cont'd

21 CFR 812 Supbart G

- Maintain adequate **records**
  - Correspondence
  - Investigator Agreements
  - Device Disposition
  - Adverse effects and complaints
- Grant **inspections** to FDA (establishments and records)
- Prepare and submit **reports**
  - Unanticipated adverse device effects
  - Withdrawal of IRB Approval
  - Current Investigator list
  - Progress reports
  - Recall and device disposition
  - Final report
  - Failure to obtain informed consent
  - Significant risk device determinations

Investigator Responsibilities
21 CFR 812 Subpart E

- **Conduct investigation** per signed agreement, investigational plan, FDA regulations and conditions of approval
- **Protect** rights, safety, and welfare of **subjects** under care
- **Control** of investigational **devices**
  - Supervise device use, appropriate disposal
- Obtain appropriate **informed consent**

Investigator Responsibilities Cont'd

21 CFR 812 Supbart G

- Maintain adequate **records**
  - Correspondence
  - Subject case history
    - Case report forms, consent, medical records
  - Device Disposition
  - Adverse effects and complaints
  - Protocol
- Grant **inspections** to FDA (establishments and records)
- Prepare and submit **reports** (to sponsor, IRB)
  - Unanticipated adverse device effects
  - Withdrawal of IRB Approval
  - Progress reports
  - Final report
  - Failure to obtain informed consent
  - Protocol deviations

Institutional Review Boards - 21 CFR 56

- Purpose: to protect the rights and welfare of human subjects involved in FDA-regulated investigations and investigations that support applications for research (e.g. IDEs) or marketing permits
  - Risk determination, Review of protocols and informed consent, Review of changes to protocols, Continuing review
- An IRB must comply with the IRB (Part 56) and IDE (Part 812) regulations
- FDA does periodic inspections of the IRB's records and procedures to determine compliance with the regulations

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Providing Industry Education

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   - comprehensive regulatory information on premarket and postmarket topics

   http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance
3. **Division of Industry and Consumer Education (DICE)**
   - If you have a question - Email: DICE@fda.hhs.gov
   - Phone: 1(800) 638-2014 or (301) 796-7100 (Live Agents 9am – 4:30 pm EST)

   Web Homepage:

   http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/ContactUs--DivisionofIndustryandConsumerEducation/default.htm

Thank you