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?

Device Study

Exempt

Not Exempt

Significant Risk (SR)

Non-Significant Risk (NSR)

Full requirements

Abbreviated requirements
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?

- **Device Study**
  - **Exempt**
  - **Not Exempt**
    - **Significant Risk (SR)**
    - **Non-Significant Risk (NSR)**

*Abbreviated requirements*
*Full requirements*
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”
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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.
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”
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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
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 Subpart 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

1. CDRH Learn – Multi-Media Industry Education
   - over 80 modules - videos, audio recordings, power point presentations, software-based “how to” modules
   - accessible on your portable devices http://www.fda.gov/Training/CDRHLearn

2. Device Advice – Text-Based Education
   - 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