



# Clinical Trials and Investigational Device Exemptions

**FDA Small Business  
Regulatory Education for Industry (REdI)  
Silver Spring, Maryland  
September 29, 2015**

**Soma Kalb, Ph.D.**

Director

Investigational Device Exemption Program

Office of Device Evaluation

Center for Devices and Radiological Health

U.S. Food and Drug Administration



# 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 CDRH's efforts to strengthen the clinical trials enterprise

# Overview

- What is an IDE?
- FDA Decisions for IDE Clinical Investigations
- The Clinical Trials Program

# Overview

- **What is an IDE?**
- FDA Decisions for IDE Clinical Investigations
- The Clinical Trials Program

# 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) $\Rightarrow$ 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

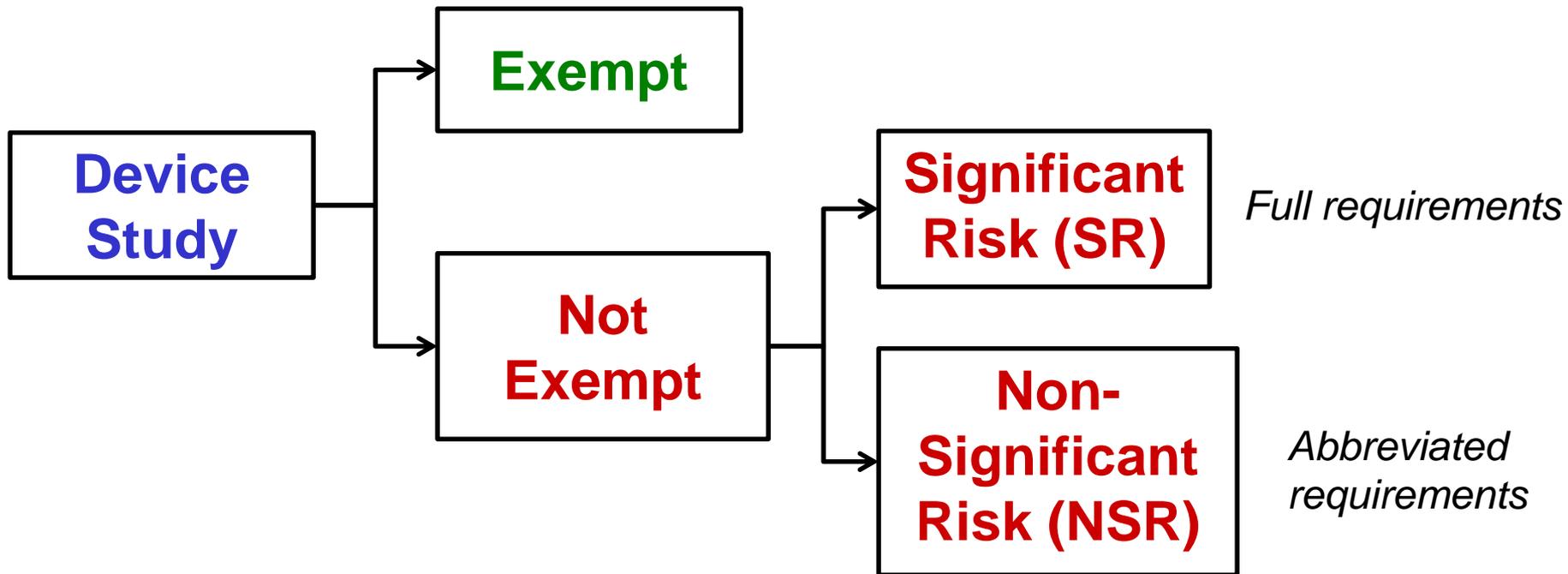
# Studies Subject to the Regulation

- To support marketing application [PMA, HDE or 510(k)]
- For collection of safety and effectiveness information (e.g., a new intended use of a legally marketed device)
- Sponsor-investigator studies of unapproved devices or new intended use of approved device (even if no marketing application planned)

# Types of Studies

- **Pivotal Study**
  - Collects definitive evidence on safety and effectiveness for a specified intended use, typically in a statistically justified number of subjects
- **Feasibility Study**
  - Captures preliminary safety and effectiveness data in a small number of subjects
  - Traditional: Inform design of pivotal study
  - Early: Inform device design

# 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
  - if not for the purpose of determining safety or effectiveness and not putting subjects at risk:
- Veterinary devices
- 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

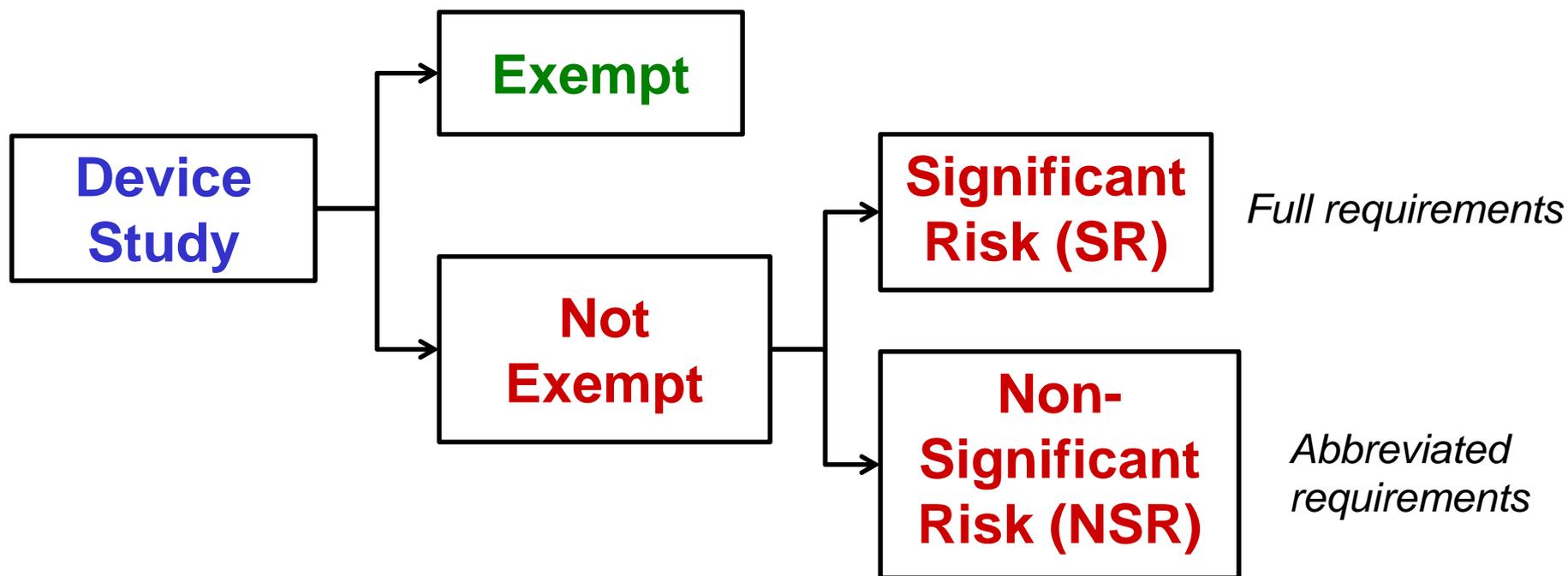
# “Practice of Medicine”

- 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
- Only using the device to address the research question
- Not evaluating the safety/effectiveness of the device
- **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)

# Non-Exempt Studies

- **Non-Significant Risk** – no IDE submission to FDA needed
  - abbreviated requirements
    - Labeling (812.5)
    - IRB Approval (56)
    - Informed Consent (50)
    - Monitoring (812.46)
    - Records and Reports (812.140(b)(4) and (5), 812.150(b)(1) - (3) and (5) - (10))
      - Annual and Final Progress Reports are not required
    - Promotion (812.7)
- **Significant Risk** – Study can not begin until IDE is approved by FDA

# 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 all participants in clinical investigation

# 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 (example, listing, certification)
- 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 IDE Application

- FDA sends acknowledgement with IDE number: GYYxxxxx (e.g., G150001)
- 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
  - Enrollment and follow-up completion
  - Withdrawal of IRB or FDA approval
  - Current list of investigators
  - Final report

# Overview

- What is an IDE?
- **FDA Decisions for IDE Clinical Investigations**
- The Clinical Trials Program

# 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
  - Deficiencies will be listed
  - 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 (21 CFR 812.30(b)(1)).
- The application contains an **untrue statement** of material fact, or **omits** material information (21 CFR 812.30(b)(2)).
- The sponsor **fails to respond** to a request for additional information (21 CFR 812.30(b)(3)).
- There is reason to believe that the **risks are not outweighed by the anticipated benefits to the subjects and the importance of the knowledge to be gained, or informed consent is inadequate, or the investigation is scientifically unsound, or the device as used is ineffective** (21 CFR 812.30(b)(4)).
- It is otherwise unreasonable to begin due to the way the device is used or the inadequacy of **(i) the report of prior investigations or the investigational plan; (ii) the manufacturing, processing, packaging, storage, and/or installation of the device; or (iii) monitoring and review of the investigation.** (21 CFR 812.30(b)(5)).

# 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, July 2012

- 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), HDE, or de novo classification.
- **Disapproval** is based on concerns related to subject safety and protections

# Other Elements of FDA Decisions/Letters

## “Staged Approval”

- Considered a full approval or approval with conditions
- FDA will grant approval or approval with conditions for a *portion* of the planned subject cohort while the particular outstanding questions are addressed
- A staged clinical investigation may be appropriate to allow initiation of subject enrollment in a study while providing additional mitigation of risk by limiting exposure of the investigational device to a smaller subject population
- Study expansion is requested by the sponsor once additional information addressing outstanding questions is submitted to FDA

# Other Elements of FDA Decisions/Letters

## Study Design Considerations

- Recommendations (but not requirements) regarding study design to help study achieve its goals
  - Example: In your study of the Heart Failure Magic device, you are proposing to measure effectiveness using the 6 minute hall walk test. As blinding is not possible with this device, FDA has concerns about bias introduced in your study results by placebo effect. FDA recommends that you modify your effectiveness endpoint to assess a more objective measure of effectiveness.

# Other Elements of FDA Decisions/Letters

## Future Considerations

- Issues relevant for future submissions
  - Example: In conducting a future pivotal study, a different study design may be more appropriate as the advantage of the cross-over study design that you have proposed is not clear. In a cross-over design, order effects and carry-over effects may be problematic for comparing the two groups. Data collected in your feasibility trial should help to determine the extent of these effects and to design an appropriate pivotal study.

# 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.
- *“FDA Decisions for Investigational Device Exemption (IDE) Clinical Investigations”*

# Overview

- What is an IDE?
- FDA Decisions for IDE Clinical Investigations
- **The Clinical Trials Program**

# CDRH 2014/2015 Strategic Priorities

- Strengthen the Clinical Trial Enterprise
  - **Goal:** Improve the efficiency, consistency, and predictability of the IDE process to reduce the time and number of cycles needed to reach appropriate IDE full approval for medical devices, in general, and for devices of public health importance, in particular.
  - **Goal:** Increase the number of early feasibility/first-in-human IDE studies submitted to FDA and conducted in the U.S.

# What has CDRH done?

- Established Clinical Trials Program and Clinical Trials Director (CTD)
- Established Early Feasibility Study (EFS) Coordinators within Clinical Trials Program
- Established SOP for CTD involvement and review of certain IDE decisions. Focus on:
  - Ensuring CDRH is “in the right place”
  - Ensuring flexibility is applied where appropriate
  - Increased communication with sponsors

# SOP Policy and Scope

- IDE approvability decisions typically made at Division level.
- With SOP, 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

Round

**1**



CTD reviews and provides feedback



Review team  
offers telecon  
to clarify rationale

# SOP Provisions

Round

**1**



Review team offers telecon to clarify rationale

CTD reviews and provides feedback

Round

**2**



CTD included in 10-day telecon

# SOP Provisions

Round

**1**



Review team offers telecon to clarify rationale

CTD reviews and provides feedback

Round

**2**



CTD included in 10-day telecon

Round

**3+**

Consultants provide review in 14 days



CTD included in 10-day telecon

CTD notified 5 days prior to decision letter

Review team notifies CTD that response is under review

# SOP Outcomes

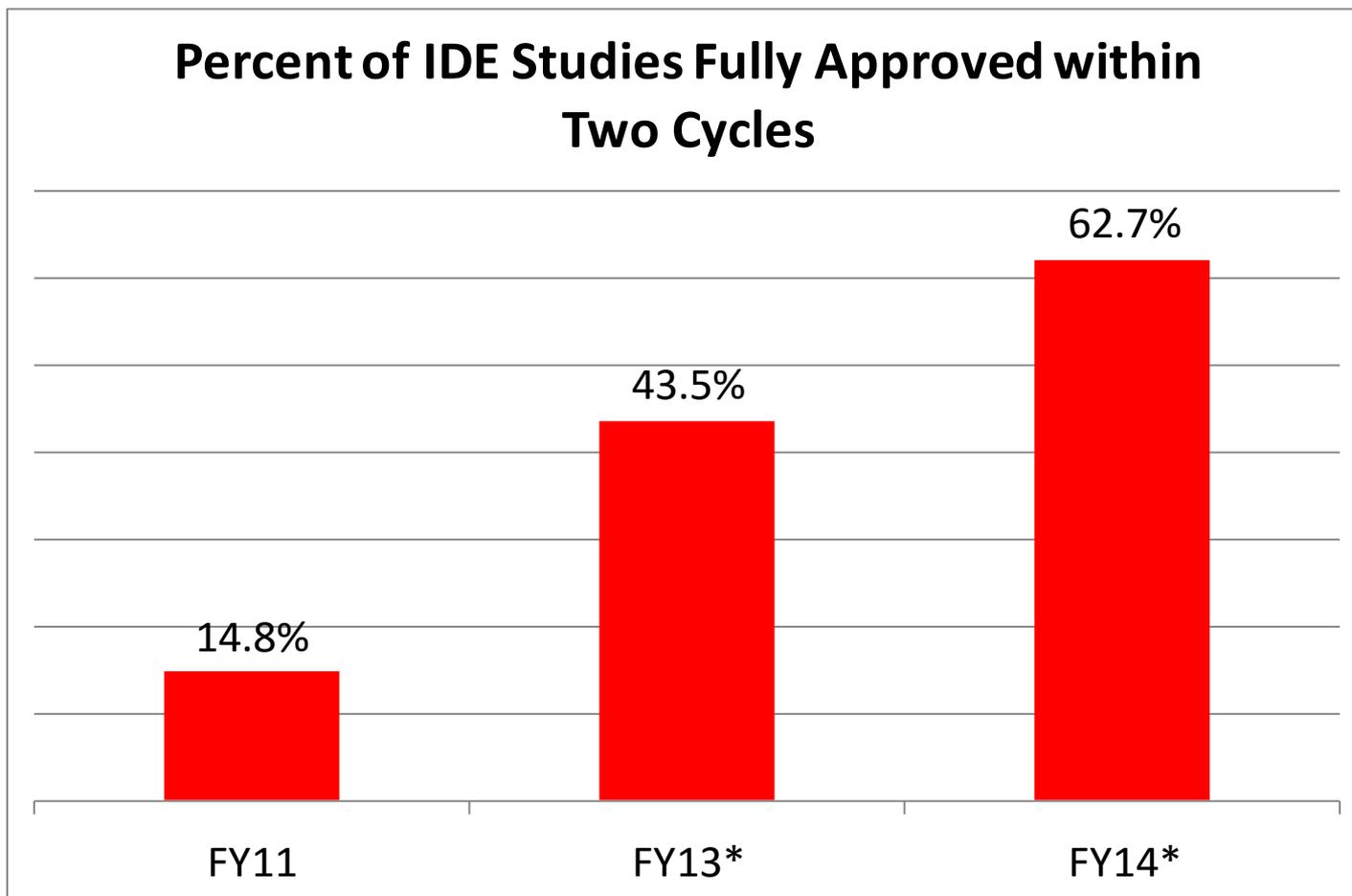
- Helps ensure consistency in decision-making
- Facilitates sharing of best practices across divisions
- Encourages higher levels of interaction
- Helps prepare sponsor to respond
  - 10-day meeting
  - “Outside” perspective on letter

# FY2014 Goals and Results

By September 30, 2014, compared to FY13 performance, CDRH sought to:

- Reduce the number of IDEs requiring more than two cycles to an appropriate full approval decision by 25%
  - Result: 34% reduction
- Reduce the overall median time to appropriate full IDE approval by 25%
  - Result: 53% reduction

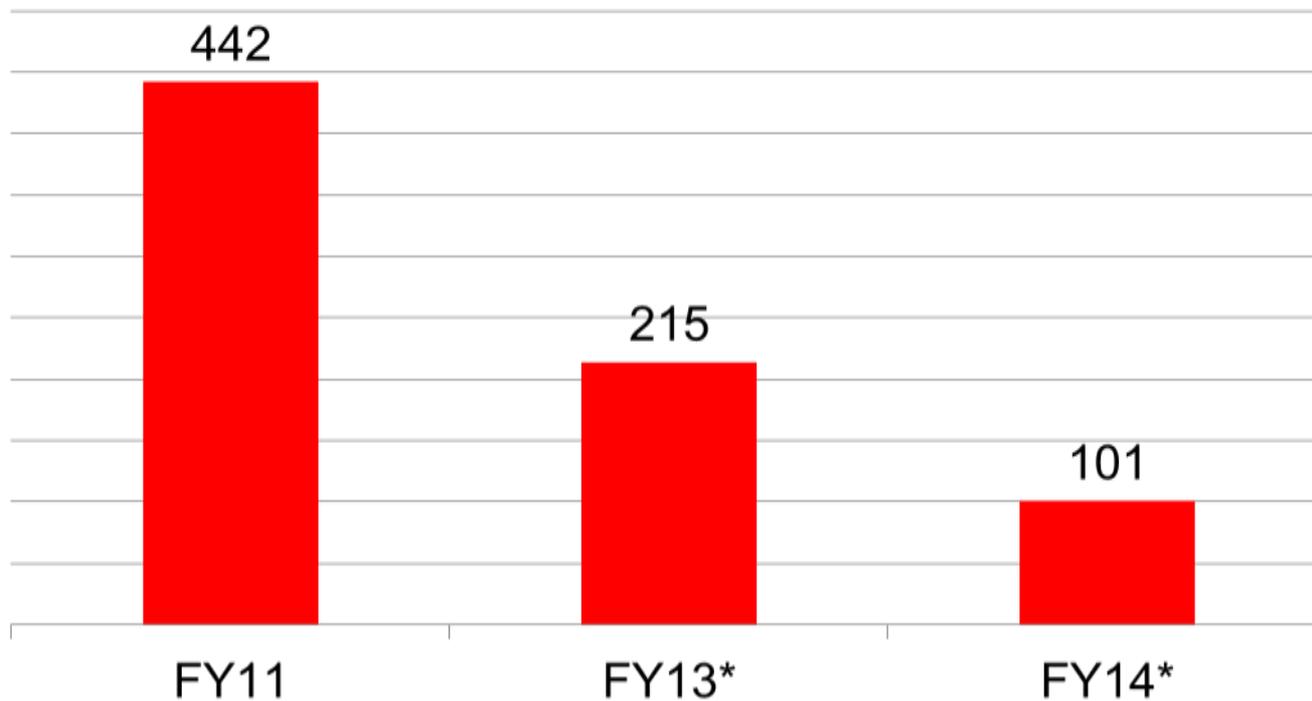
# FY14 Performance



\* Values calculated on 10/31/13 and 10/31/14 respectively

# FY14 Performance

## Median Days to Full IDE Study Approval



\* Values calculated on 10/31/13 and 10/31/14 respectively

# FY2015 Goals

By June 30, 2015, compared to FY13 performance, CDRH seeks to:

- Reduce the number of IDEs requiring more than two cycles to an appropriate full approval decision by 50%
- Reduce the overall median time to full appropriate IDE approval to 30 days.
- Increase the number of early feasibility/first-in-human IDE studies submitted to each premarket Division

# FY15 Efforts to Achieve Goals

- Incorporate benefit-risk principles for IDEs
- Focus on Submission Quality
- Advance Early Feasibility Program efforts

## **Draft Guidance:**

# ***Factors to Consider When Making Benefit-Risk Determinations for Medical Device IDEs***

- Clarify the factors that FDA considers when assessing risks and anticipated benefits for IDE studies
- Degree of acceptable uncertainty and level of risk should consider:
  - Seriousness of the disease or condition
  - Potential benefits to subjects and importance of knowledge to be gained
  - Risk mitigations
  - Alternative treatments available
  - Stage of study
  - Patient preference and tolerance for risk

# Submission Quality

- Many IDE submissions fail to “tell the sponsor’s story”
- Many others fail to provide basic information needed to support FDA’s IDE review
- Interaction with sponsor during IDE review can help resolve minor issues, but improvements in submission quality are a critical component as well

# Major Nonclinical Reasons for IDE Deficiencies

- Device description
- Mechanical testing
- Biocompatibility
- Animal testing

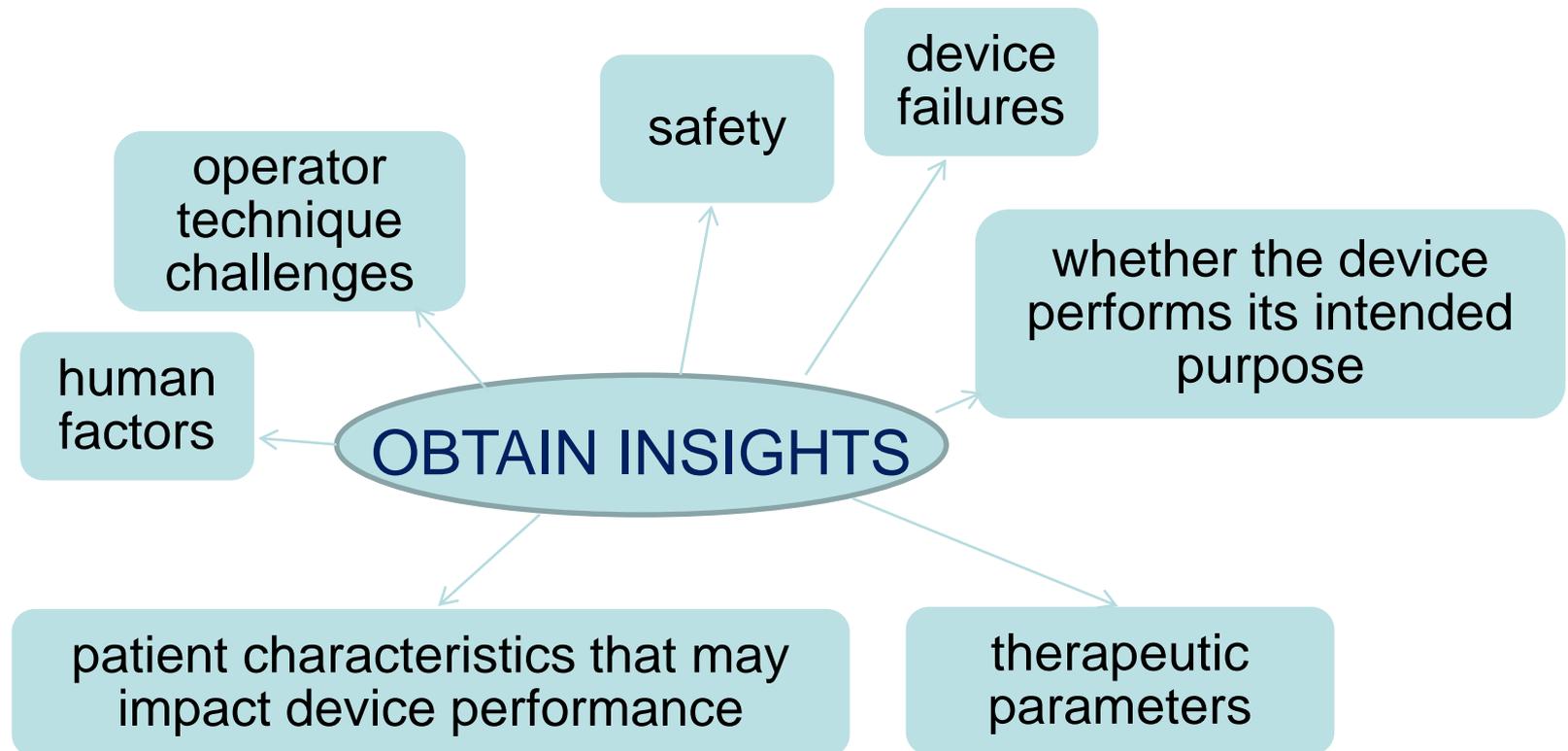
# Types of Questions that relate to Submission Quality

- Describe device components and materials
- Describe principle of operation and key characteristics
- Clarify version of device tested compared to version for clinical study
- Clarify what testing was done with rationale
- Provide adequate description of test conditions, success criteria, and results

# Early Feasibility Study (EFS) Program

- **Intent** - To facilitate US EFS under the IDE regulations
- **Scope** - Elements that define an early feasibility study:
  - Small number of subjects
  - Device that may be early in development, typically before the device design has been finalized
  - Does not necessarily involve the first clinical use of a device

# Purpose of Early Feasibility Studies



# Why Focus on EFS?

- **EFS is often a critical step in device innovation and development.**
- When EFS are conducted in the US, important new technologies may become available to US patients sooner.

# EFS Guidance

- **Key Guidance Principle** - Approval of an early feasibility study IDE may be based on less nonclinical data than would be needed to support the initiation of a larger clinical study of a more final device design
- **Guidance Provisions** - A regulatory toolkit that enables sponsors and regulators to think in new ways about device development
  - Justifying the appropriate evidence needed to move from bench to clinical study
  - Allowing timely device and clinical protocol modifications

# Summary

- IDE statutes and regulations encourage discovery and development of medical devices while protecting public health and safety
- With FDASIA, IDE decision letters have been re-structured to permit timely commencement of IDE studies, while protecting subjects
- CDRH Strategic Priorities aim to strengthen the clinical trials enterprise through formal Office-level review of challenging IDEs and promotion of early feasibility studies.

# Resources

- Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors

<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm113709.htm>

- Frequently Asked Questions About Medical Devices
- Significant Risk and Nonsignificant Risk Medical Device Studies

- Guidance: Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions (IDEs)

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM451440.pdf>

# Resources

- Guidance: FDA Decisions for IDE Clinical Investigations  
<http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279107.pdf>
- Standard Operating Procedures Review of IDE Application-Specific Issues
- <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm384135.htm>
- Guidance: IDEs for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies  
<http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279103.pdf>

# Industry Education Resources

## Three 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

<http://www.fda.gov/Training/CDRHLearn>

### 2. Device Advice – Text-Based Education

- comprehensive regulatory information on premarket and postmarket topics

[www.fda.gov/MedicalDevices/DeviceRegulationandGuidance](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance)

### 3. Division of Industry and Consumer Education (DICE)

- Contact DICE if you have a question
- Email: [DICE@fda.hhs.gov](mailto:DICE@fda.hhs.gov)
- Phone: 1(800) 638-2014 or (301) 796-7100 (Hours: 9 am-12:30 pm; 1 pm-4:30pm EST)
- Web: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/ContactUs--DivisionofIndustryandConsumerEducation/default.htm>

# Questions?

Please complete the session survey:  
[surveymonkey.com/r/DEV-D1S3](https://surveymonkey.com/r/DEV-D1S3)