



Clinical Trials and Investigational Device Exemptions

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January 20, 2015



Clinical Trials and IDEs

- Regulatory context
- Provisions of the IDE regulations and overview of IDE studies
- Discussion of when is an IDE needed
- The IDE application
- Roles of sponsors, investigators, and IRBs
- Hot topics in IDEs



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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



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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



Types of Studies

- Unapproved device
- Approved device for a new indication (off-label use)
- Manufacturer-sponsored vs. Academic-sponsored
 - Intent to market?

Types of Studies

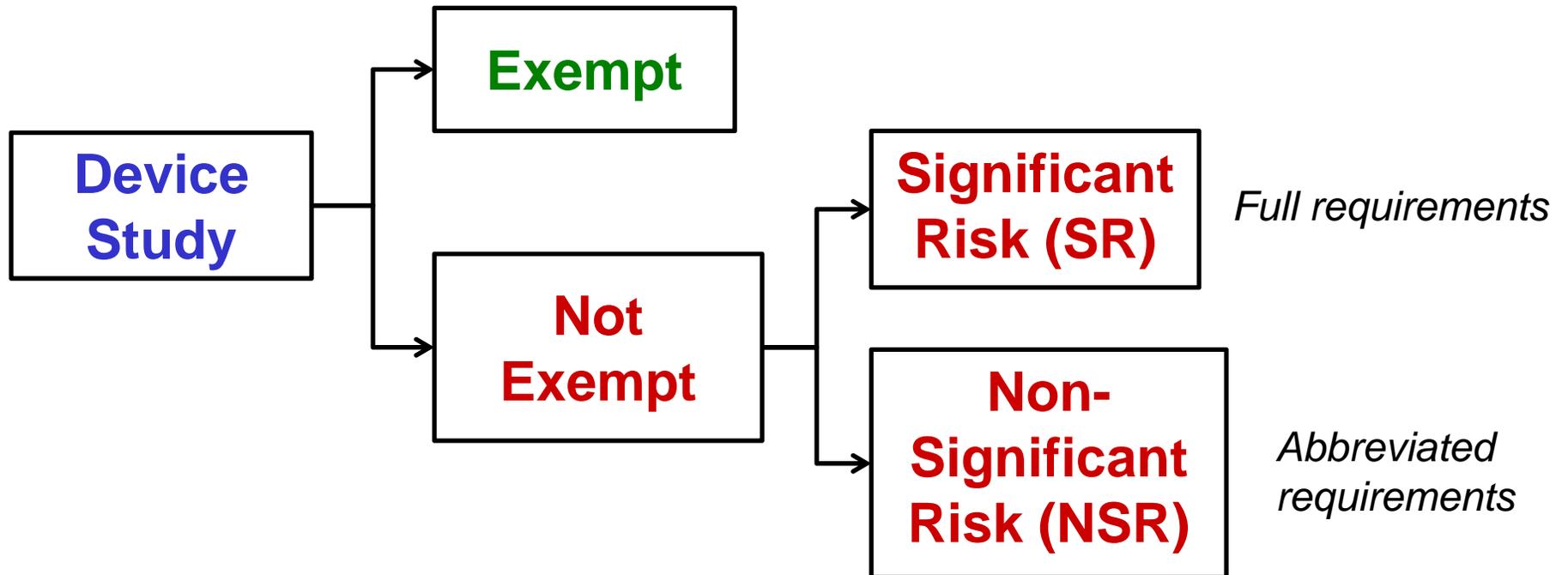
- Pivotal Study
 - Designed to collect definitive evidence on safety and effectiveness for a specified intended use, typically in a statistically justified number of subjects
- Feasibility Study
 - Capture preliminary safety and effectiveness data in a small number of subjects
 - Traditional: Inform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



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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”

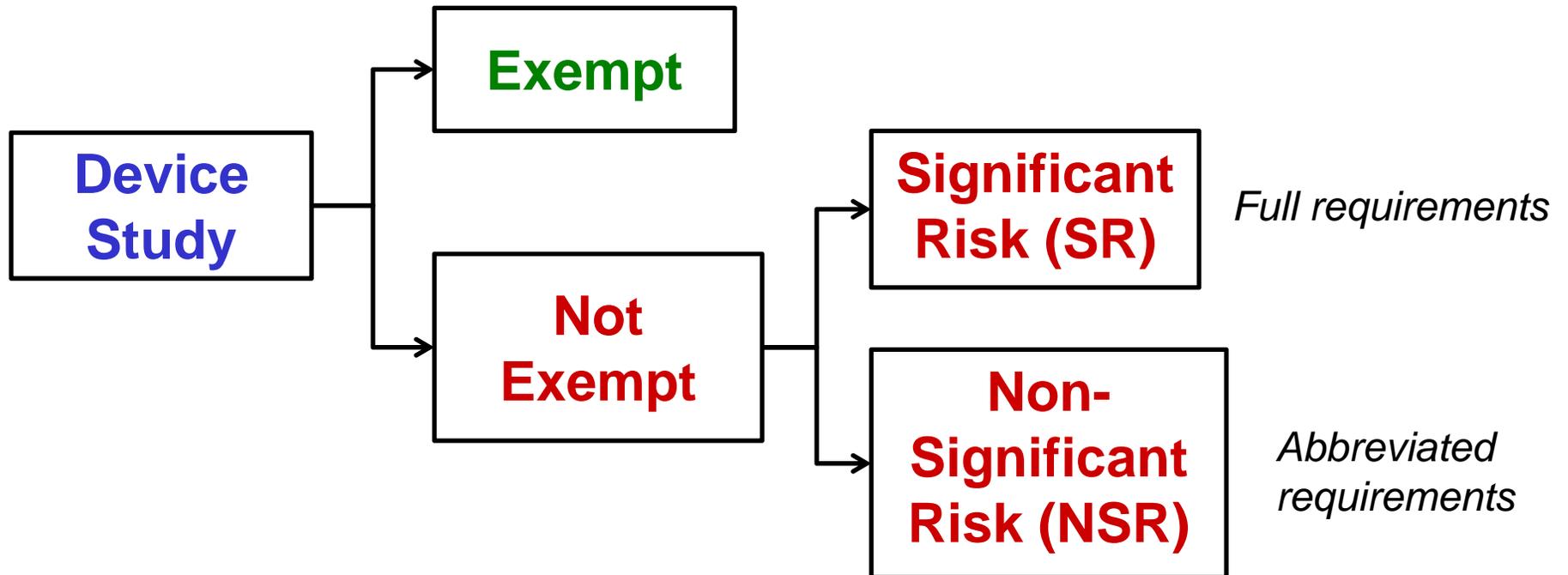
- Physician should:
 - Be well informed about the product
 - Use firm scientific rationale and sound medical evidence
 - Maintain records on use and effects
- **IDE not required**; institution may require IRB review/approval and informed consent
- Other prohibitions still apply



“Basic Physiological Research”

- Investigating a physiological principle
- 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)

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



Risk Determination

- **Sponsor** makes initial determination
- **IRB reviews** the sponsor's determination (21 CFR 812.2(b)(1)(ii))
 - 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)
- FDA is available to help

Non-Significant Risk

- 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
 - **Abbreviated** IDE requirements (labeling, IRB, consent, monitoring, reporting, prohibition on promotion)
 - **No IDE** submission to FDA needed



Significant Risk Studies

- **Full IDE** requirements apply
- Sponsor submits IDE application to FDA
- FDA renders **decision** within 30 calendar days
- If approved, sponsor obtains **IRB approval**
- After **both FDA and IRB** approve the investigation, study may begin



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; IRB does not need to conduct an independent assessment of risk

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



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Device Studies

- Trials tend to be smaller than drug trials
- Many not blinded or randomized
- Many are not controlled
- Some novel, many “me-too”
- Adaptive designs increasingly common
- Endpoints highly diverse
- Typically, single pivotal trial follows feasibility stage(s)



Sponsor-Investigator Studies

- Investigator assumes responsibilities of both the sponsor and the investigator
- Not intended to support a marketing application
- May be used to answer research questions or to support future studies
- Endpoints and sample size may not be statistically driven
- Single site or multiple sites



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



Basic Submission Elements

- Background of medical issue, the study goals, and why this study will further the science



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- Detailed description of the device under study



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- Background of medical issue, the study goals, and why this study will further the science
- Detailed description of the device under study
- Previous studies (preclinical and clinical)
 - Summary of available data
 - Why is a clinical study needed at this stage?
 - Are there outstanding safety questions that should be addressed with preclinical data?
 - What evidence supports the safety of this study/device and the potential for the study data to be meaningful?



Basic Submission Elements

- Risk analysis
 - What are the potential risks to the patient?
 - Does the study mitigate the risks where possible?
 - Are the risks outweighed by the potential for benefit and/or value of the study



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- Inclusion and exclusion criteria
- Study objectives or endpoints
- Patient monitoring and follow-up plan



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 - Are the risks outweighed by the potential for benefit and/or value of the study
- Inclusion and exclusion criteria
- Study objectives or endpoints
- Patient monitoring and follow-up plan
- Sample size and number of investigational centers, with justification
- Informed consent document



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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
- Review is comprehensive



FDA Review Considerations

- Industry-Initiated Pivotal study
 - Are patients adequately protected?
 - Does the study design support the desired labeling claims?
- Sponsor-Investigator Study
 - Are patients adequately protected?
 - Does the potential benefit or value of the data justify the risk?



FDA Review Considerations

- Reasonable study conceptually?
- Adequate preclinical validation of device?
- Appropriate enrollment criteria?
- Appropriate mitigation of potential risks?
- Patients adequately informed?
- Is bias adequately minimized?
- Sample size appropriate?



Common Pitfalls

- Inadequate detail regarding the device or the methods used in the study
- Inadequate basic safety/performance data
- Inadequate justification for why clinical data are truly needed at this stage.
- Inadequate procedures in place (or discussion of those procedures) to maximize patient safety
- Inadequate informed consent document



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



Recent 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

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 Decision Letters

- **Future considerations**
 - Issues relevant for future submissions

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?



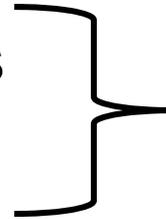
Approval



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”*



Responses to Deficiencies

- Submitted as Amendments
- Cover letter identifies G#, date of letter
- Typical format addresses deficiencies one by one, in order:
 1. *{Restate FDA deficiency #1}*
Sponsor Response:
 2. *{Restate FDA deficiency #2}*
Sponsor Response
- Reviewed within 30 days
- If deficiencies not fully addressed, another approval with conditions (or disapproval) may be issued



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



FDA Review of Supplements and Reports

- Supplements
 - Approval, Approval with Conditions, Disapproval
- Reports
 - Report Ok, Report Deficient
- Responses to any deficiency letters are submitted as amendments, referencing the parent document
- All have 30 day review clock



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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

21 CFR 812 Subparts A,C

- 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 labeling, prohibition of promotion, import and export requirements (Subpart A).



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 Subpart 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
 - Protocol deviations
 - Final report
 - Failure to obtain informed consent



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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 is CDRH doing to achieve this?

- Established Clinical Trials Program and Clinical Trials Director (CTD)
- 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
- Established Early Feasibility Study (EFS) coordinators within Clinical Trials Program



SOP Provisions

Review of Investigational Device Exemption (IDE)

Application-Specific Issues: Standard Operating Procedure issued on February 5, 2014, Effective date March 1, 2014

- 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



FY2014 Goals

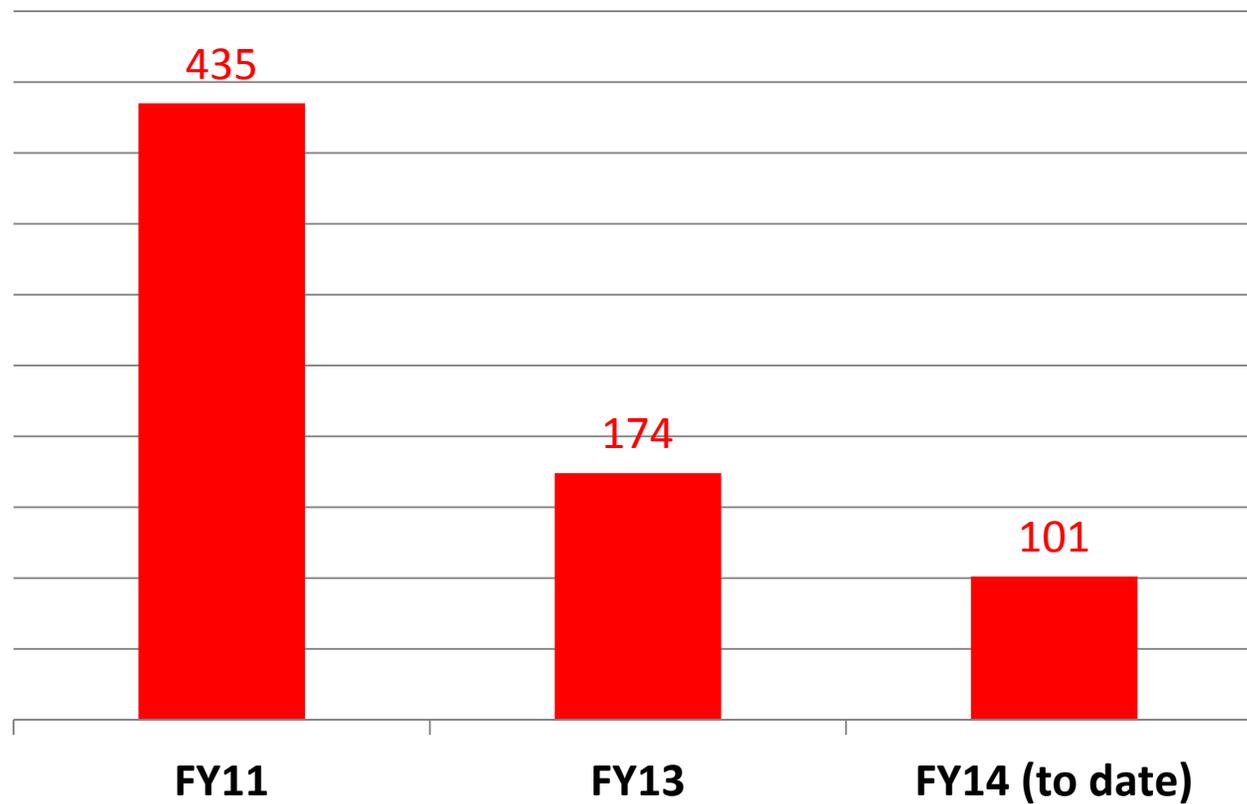
By September 30, 2014, compared to FY13 performance, CDRH seeks to:

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



Recent Performance

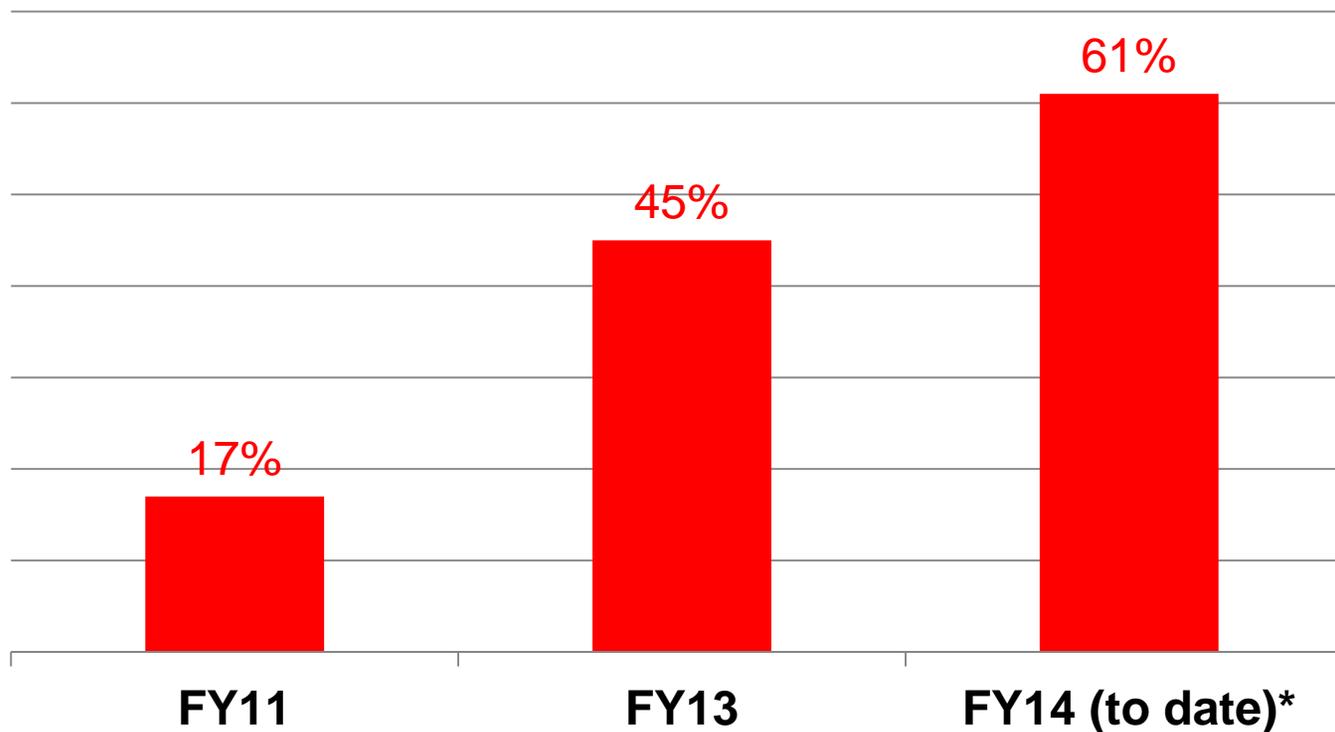
Median Days To Full IDE Approval





Recent Performance

Percent of IDEs fully approved within two cycles



* This is a conservative estimate of the current FY14 performance since it assumes that all IDEs that have not yet completed two cycles of review will not be approved within two cycles

Early Feasibility Study (EFS) Program

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



Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies

- Guidance issued on October 1, 2013
- **Key Guidance Principle** – 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 Provisions** – New ways to think about:
 - Device development
 - Justifying the appropriate evidence needed to move from bench to clinical study
 - The implementation of timely device and clinical protocol modifications

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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

- Device Advice:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm>

- CDRH Learn:

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



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>



Contact Information

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