



# The Investigational Device Exemption (IDE)

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# Review of Product Development Process for Medical Devices

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- Product specifications: components
- Classification of medical devices; controls
- Testing: nonclinical/bench and animal
- Clinical Testing: IRBs, IDEs
- Pilot plant - scale up - manufacturing
- Quality Assurance: clinical, manufacturing
- 510(k) or PMA Application

# When are Clinical Studies Required



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- Guidance document so states
- Unresolved issues in preclinical studies
- Safety concerns
- Demonstration of clinical utility (FDA request)
- Predicate product submission contained clinical data
- Feasibility; proof of concept
- (Optional) for marketing evaluation, “seeding” and/or fundraising purposes



# Clinical Testing - Feasibility

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Usually done in 3 stages: feasibility, pilot, pivotal

- Feasibility test; proof of concept:
  - 3-5 subjects
  - one site
  - usually investigator-sponsored



# Clinical Studies - Pilot

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- Pilot test protocol
  - 10-30 subjects
  - one or two sites
  - “test drives” protocol and operator’s manual
  - usually industry-sponsored IDE



# Clinical Testing - Pivotal

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- Pivotal Study
  - consult guidance document, if any (may be on type of product or disease/clinical condition)
  - number of subjects varies
    - experiential study
    - confirmatory study
    - statistically significant study
  - multiple sites (at least 3)
  - duration depends on length of human exposure to device



# Clinical Studies - 3

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- Types of study designs for different class products
  - Class I – clinical studies not required
  - Class II – comparative study; usually vs. predicate(s) to support 510(k)
  - Class III: prospective, randomized, well-controlled; demonstrating device is safe and effective for its intended use: used to support a PMA



# Safety and Effectiveness

## 21 CFR 860.7

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- Considerations:
  - Persons for whom the device is intended
  - Conditions of use for the device
  - Possible benefit to health vs. probable injury or illness from use
  - Reliability of the device
- Reliance on valid scientific evidence only (may include objective performance criteria)



# Valid Scientific Evidence

21 CFR 860.7(c)(2)

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- Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. The evidence required may vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use.



# What Valid Scientific Evidence is **NOT**

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- Isolated case reports and testimonials
- Random experience
- Unsubstantiated opinions
- Reports lacking sufficient details to permit scientific evaluation



# Links to Items of Important Considerations in Clinical Trials

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- Selection of Investigators/Sites  
<http://www.fda.gov/cdrh/comp/2229.html>
- Financial Disclosure <http://www.fda.gov/oc/guidance/financialdis.html>
- IRB Review and Approval  
<http://www.fda.gov/cdrh/devadvice/ide/irb.shtml>
- Informed Consent  
[http://www.fda.gov/cdrh/devadvice/ide/informed\\_consent.shtml](http://www.fda.gov/cdrh/devadvice/ide/informed_consent.shtml)
- Monitoring  
[http://www.fda.gov/ora/compliance\\_ref/bimo/clinguid.html](http://www.fda.gov/ora/compliance_ref/bimo/clinguid.html)
- Clinical Auditing  
[http://www.fda.gov/ora/compliance\\_ref/bimo/7348\\_811/default.htm](http://www.fda.gov/ora/compliance_ref/bimo/7348_811/default.htm)
- Data Management and analysis



# Significant Risk Devices

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- Significant risk device: one which presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is an implant, (2) is used in supporting or sustaining life, (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or (4) otherwise presents a potential for serious risk



# Nonsignificant Risk Devices

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- Non-significant risk device: one that does not meet the definition of a significant risk device
  
- [fda.gov/cdrh/d861.html](http://fda.gov/cdrh/d861.html)



# Initial FDA Submission

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- May need only IRB approval to proceed with study on non-significant risk device, i.e., no prior FDA approval to conduct study
- Investigational Device Exemption (IDE) needed for significant risk device or condition of use
- IDE may be needed for studies on some Class II (510[k]) and all Class III (PMA) products



# IDE Contents - 1

## (21 CFR 812.20)

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- Cover sheet
- Table of contents
- Report of prior investigations
- Investigational plan
- Methods, facilities and controls for manufacturing, packaging, storing, installation
- Example of Investigator Agreements
- Certification of Investigator Agreement



## IDE Contents - 2

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- IRB information
- Other institutions studying the device that are not listed above
- Sale or charges for investigational device
  - why not considered commercialization
- Environmental assessment
  - or request for categorical exclusion



# IDE Contents - 3

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- Labeling
  - labels
  - instructions for use; operator's manual
  - training materials
- Informed consent documents
- Other relevant information, as requested by FDA



# Investigational Plan

## (21 CFR 812.25)

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- Name and intended use of the device
- Objectives and duration of the investigation
- Protocol [CRFs]
- Risk analysis
- Device description
- Monitoring procedures
- Labeling
- Consent materials [patient, guardian, etc.]
- IRB information
- Other institutions
- Additional records and reports



# Medical Device Tracking

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- Discuss with FDA if your device will need to be tracked after IDE is closed
- Be prepared with a plan to do this
  - What information is required
  - Where data will be kept
  - Who will have the responsibility to maintain database
- Keep HIPAA considerations in mind when preparing plan



# FDA Submissions

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# Submissions and/or Reports to FDA and/or IRB that are Required while IDE is open

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- 6 month reports: update investigator list (adding, deleting, changes at site)
- Progress reports (Suggested format: <http://www.fda.gov/cdrh/dsma/311.html>)
- Reports of use of device without consent being obtained
- Adverse Device Event reports
- Protocol changes
  - Those requiring pre-approval
  - Those requiring notification



# Submissions Required for Marketing

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- Submitted to CDRH or to CBER  
(biological devices, e.g. some IVD kits, immunoadsorption columns)
- Devices and *in vitro* diagnostics:
  - Premarket Notification (510[k]) - receive a K number (CDRH) or a BK number (CBER)
  - Premarket Approval Application (PMA) - receive a P number (CDRH) or a BP number (CBER)



# FDA Review Process

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# Items Affecting Review Process

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- IDEs and PMAs have priority
- 510(k)s and PMAs granted expedited status are reviewed first
- If additional data are requested by FDA, the application is put on hold
- Consulting review of the application may require another Division or Center



# FDA Review of IDEs

## (21 CFR 812.30)

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- Refusal to accept because
  - an IDE is not required,
  - application is incomplete
  - or fails to demonstrate scientific soundness or to meet sections 21 CFR 812.20, .25, .27 or 813.
- Possible responses
  - Approve
  - Approve with modifications
  - Disapprove



# Reasons for Disapproval of IDE (21 CFR 812.30)

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- Failure to comply with the Act or this CFR Part
- contains untrue statements or has omitted important facts
- sponsor fails to respond to request for additional information
- risks outweigh benefits
- inadequacy of manufacturing information, labeling, monitoring plans, etc.



# Extended Use IDE

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- When study is thought to be complete (i.e., met enrollment goal, but before knowing if all subjects' data will be accepted), some companies choose to keep a few sites open under their IDEs in order to continue to accrue subjects in case too many are disqualified



# Some Examples Why Subjects May Be Disqualified

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- Insufficient number of required visits, especially final visit
- No or inadequate follow-up for a subject who chose to discontinue
- No follow up or outcome for a reported adverse event
- Cannot account for all enrolled subjects
- Even if all visits made, too many significant parameters are missing, measurement not done
- Subject never met enrollment criteria
- Subject improperly or not consented



# Closing the IDE

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- Ensure all queries have been answered
- Close-out visits at sites ensures regulatory documentation is stored and retrievable for FDA pre-approval inspection
- Investigational supplies have been retrieved from sites
- Investigators write final report within 90 days
- Data base is closed; biostatistician does statistical analysis and evaluation, writes report
- Final clinical report written
- IRB is informed study is closed; applicable reports sent to IRB
- FDA is informed study is completed; final clinical report is submitted



# Medical Device Reporting

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- Even after IDE is closed, the Sponsor is still obligated to report any adverse events to the FDA
- These events will be reported to the Reviewer while the PMA or 510(k) is being reviewed. Even after the Panel recommends approval of the device, these procedures must be kept in place until after the sponsor has passed the clinical and manufacturing pre-approval inspections.
- 21 CFR § 803