

# IDE Exemption, Preparation and Maintenance

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# Templates and Guidance

- Best Practices Templates/Instructions
  - <http://tiny.cc/d7bpt>
- Recorded Webcasts
  - <http://tinyurl.com/8n34gr4>

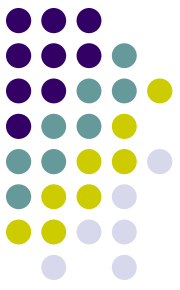




# Part 1: IND Exemptions

- Background
- Clinical Investigations of a Medical Device
- IDE Exemptions
- SR/NSR Determination and Abbreviated IDE
- Pre-Submission for Study Determination





# What is a Medical Device?

- Its an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent or other similar or related article or component part or accessory which:
  - is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease
  - is intended to affect the structure or any function of the body
  - achieve its primary intended purposes through physical action and not chemical or metabolic action



# What is an Investigational Drug?



- A drug that is not approved to be marketed in the US
- An approved drug that is not used according to its approved label
- **Note:** Practice of medicine allows a physician to use any approved drug without prior regulatory approval





# Medical Device Regulation

- Medical Device Amendment, 1976
  - Prior to 1976, investigational devices were either not reviewed or were reviewed as drugs
  - The amendment established device classifications based on risk (Class I, II, III)
  - Established the Investigational Device Exemption (IDE)

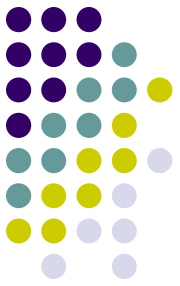




# Medical Device Classification

- Devices are classified related to the risk associated with the use of the device
  - Class I; lowest risk
  - Class II; intermediate risk
  - Class III; highest risk
  - Class I and II are considered non-significant risk (NSR) devices
  - Class III devices are considered significant risk (SR) devices





# Medical Device Classification

- Class I: dental floss, medical scissors, dental syringe
- Class II: powered wheel chair, MRI, clinical mercury thermometer
- Class III: external defibrillator, replacement heart valves, stents





# IND Exemption Assessment



- (ii) . . .the investigation is not intended to support a significant change in the advertising for the product
- (iii) the investigation does not involve a route of administration or dosage level or use in a patient population that **significantly** increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product
- (iv) the investigation is conducted in compliance with IRB and informed consent regulations
- (v) the study is conducted in compliance with regulations regarding promotion or distribution of investigational drugs





# Medical Device Classification

- Devices are classified related to medical specialties, and divided into 16 groups:
  - 21CFR 862-892
  - 862 Clinical Chemistry and Clinical Toxicology
  - 864 Hematology and Pathology
  - 866 Immunology and Microbiology
  - 868 Anesthesiology
  - 870 Cardiovascular
  - 872 Dental
  - 874 Ear, Nose, and Throat





# IND Exemption Assessment

- Device classifications:
  - 876 Gastroenterology and Urology
  - 878 General and Plastic Surgery
  - 880 General Hospital and Personal Use
  - 882 Neurology
  - 884 Obstetrical and Gynecological
  - 886 Ophthalmic
  - 888 Orthopedic
  - 890 Physical Medicine
  - 892 Radiology





# Medical Device Classification

- Devices are classified based on the date of their market introduction
  - pre-Medical Device Amendment – marketed prior to 1976
  - post-Medical Device Amendment - marketed after 1976
  - Transitional devices - those regulated as drugs prior to the 1976 MDA, but subsequently regulated as devices



# Summary of Devices Classifications



- Based on the risk
  - Class I, II & III, NSR & SR
- Based on medical specialties
  - 16 groups
- Based on date of market introduction
  - pre- , post-1976 MDA, and transitional





# Commercialization Options

- Exempt from FDA review prior to marketing
  - Most Class I and a few Class II devices are exempt from FDA review
- 510(k)
  - Part of the Food Drug and Cosmetic Act that describes device review and approval
  - Device is at least as safe and effective, or substantially equivalent to, a legally marketed device (the predicate) that is not subject to PMA
  - FDA has 90 days to review

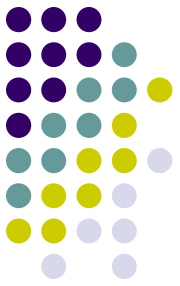




# Commercialization Options

- Pre-Market Approval (PMA)
  - A PMA application is required for all Class III devices
  - Focus on scientific and regulatory review of safety and effectiveness
  - Even if a Class III predicate exists, the device must go through a full PMA review
  - FDA has 180 days for review





# Medical Device Classification

The screenshot shows the FDA's 510(k) Premarket Notification search interface. At the top, the FDA logo and name are displayed, along with navigation links for 'A to Z Index', 'Follow FDA', and 'FDA Voice Blog'. A search bar with a 'SEARCH' button is present. Below the navigation bar, a menu lists various FDA categories: Home, Food, Drugs, Medical Devices, Radiation-Emitting Products, Vaccines, Blood & Biologics, Animal & Veterinary, Cosmetics, and Tobacco Products.

## 510(k) Premarket Notification

• FDA Home • Medical Devices • Databases

A 510(K) is a premarket submission made to FDA to demonstrate that the device to be marketed is at least as safe and effective, that is, substantially equivalent, to a legally marketed device (21 CFR §807.92(a)(3)) that is not subject to premarket approval.  
[Learn more...](#)

### Search Database

Help Download Files

510K Number:  Type:

Model:  Cleared/Approved IVD Products:

Applicant Name:  Expedited Review:

Device Name:  Third Party Reviewed:

Panel:  Product Code:

Decision:

Decision Date:  to  Clinical Trials:

Sort by:  Combination Products:

[Quick Search](#) [Clear Form](#)

### Other Databases

- Adverse Events (MAUDE)
- CDRH FOIA Electronic Reading Room
- CFR Title 21
- CLIA
- Device Classification
- Inspections
- Medsun Reports
- Premarket Approvals (PMAs)
- Post-Approval Studies
- Postmarket Surveillance Studies
- Radiation-Emitting Products
- Radiation-Emitting Electronic Products Corrective Actions
- Recalls
- Registration & Listing
- Standards
- Total Product Life Cycle
- X-Ray Assembler



# Clinical Studies Involving a Medical Device



- If the objective of the study is to assess the safety and/or effectiveness of a device, the study is subject to 21 CFR 812
  - There are exemptions whether the study must be regulated by 21 CFR 812 (more later)
  - Also, many studies use medical devices as “tools”, whose use are not the objective of the study
  - These devices would not be subject to 21 CFR 812



# Clinical Investigations of a Medical Device



- Possible options
  - The study is exempt from the IDE regulations
  - The study has an IDE approved by the FDA
  - The study has an ‘approved’ abbreviated IDE overseen only by the IRB



# Investigations Exempt from the IDE Regulations



- A legally marketed device when it is used in accordance with its labeling
- A diagnostic device meeting 4 specified criteria
- A device undergoing a consumer preference testing, testing of modification or testing of a combination of two or more devices in commercial distribution if the testing is not for the purpose of determining safety or effectiveness



# Investigations Exempt from the IDE Regulations



- A device intended solely for veterinary use
- A device for research on or with laboratory animals
- A custom device (21 CFR 812.3(b))

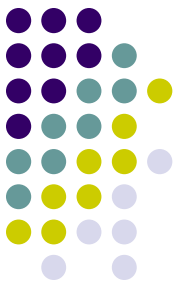




# Significant Risk Devices

- Significant Risk Device is a device that:
  - is intended as an implant and presents a potential for serious risk to the health, safety and welfare of a subject
  - is used to support or sustain human life
  - is substantial importance in diagnosing, curing, mitigating, or treating disease or otherwise preventing impairment of human health
  - otherwise presents a potential for a serious risk to the health, safety or welfare of human subject





# **Significant Risk Device Studies**

## **Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors**

### **Significant Risk and Nonsignificant Risk Medical Device Studies**

<http://tinyurl.com/48ywrw8>

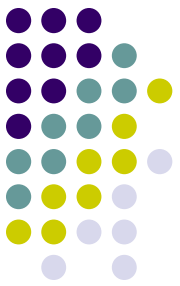




# Abbreviated IDE

- Investigator provides an initial risk determination to the IRB
- If IRB agrees with the investigator, study can be conducted as an approved abbreviated IDE with only IRB oversight
- The FDA does not need to be consulted





# Abbreviated IDE Requirements

- Obtain and maintain IRB approval of the investigation
- Make sure that the device is properly labeled
- Ensure that informed consents are obtained
- Maintain required records and reports
- Monitor the study to ensure compliance with the protocol and protect the human subject
- The promotional practices are not permitted





# Process for Study Determination



- Informal: Email/Call FDA
  - Provide protocol and risk assessment
- Formal: Pre-Submission Study Determination Request
  - Include device information and clinical protocol
  - Provide cover letter and risk assessment
  - Response within 60 days (binding determination)
- Formal: Submit full IDE
  - Response within 30 days



# Pre-Submission Process



- A formal written request from an applicant for feedback from FDA to be provided in the form of a formal written response or a meeting/teleconference
- This used to be called a Pre-IDE meeting
- However, FDA recognized that investigators/sponsors would benefit from meetings with FDA even if their study would not require an IDE
  - <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf>





# Pre-Submission Process

- Similar to pre-IND meeting for drugs
- A mechanism to obtain feedback from FDA on protocols and other aspects of device development
- Written submission of intended use, device description, protocol/plan, questions
- Encouraged, but not required, by FDA
- Can be used even if no IDE will follow
- Can be used more than once, unlike the formal Pre- IND meeting in drug development





# Pre-Submission Process

- Recommended contents for pre-sub package
  - Cover letter
  - TOC
  - Device Description
  - Proposed Intended Use
  - Previous Discussions or Submissions
  - Overview of Product Development
  - Specific Questions
  - Mechanism for Feedback





# PART 2: IDE Preparation and Maintenance





# Overview

- IDE Preparation and Submission
- IDE Maintenance
- In Vitro Diagnostic (IVD) Devices
- Additional Type of Device Studies
- Case Studies





# IDE Content (21 CFR 812.20(b))

- 1. Cover Sheet – form 3514
- 2. Name and Address of the Sponsor
- 3. Report of Prior Investigations
- 4. Investigational Plan
- 5. Manufacturing Information
- 6. Investigators Agreement
- 7. Investigators Certification
- 8. IRB Information





# IDE Content (21 CFR 812.20(b))

- 9. Name and Address of Investigators Institution
- 10. Financial Claims
- 11. Environmental Assessment
- 12. Labeling
- 13. Informed Consent
- 14. Additional Information
- <http://tinyurl.com/psf26l7> (IDE template)





# Cover Sheet – Form 3514



- Use is optional
- Form is used for IDE, 510(k), PMA, submissions
- Captures the following information:
  - Original submission, amendment, report or supplement
  - Device information (name, intended use)
  - Sponsor and manufacturer contact info
  - Previous discussion with the FDA

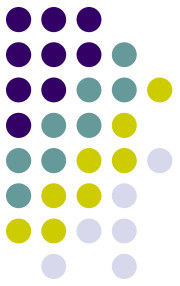


# 3. Report of Prior Investigations



- 21 CFR 812.27
- Prior clinical, animal and laboratory testing
  - If laboratory studies are referenced, statement whether such a studies have been done according to GLP
- Bibliography of all publications
- Summary of all unpublished information





## 4. Investigational Plan

- 21 CFR 812.25
- Purpose – name and intended use
- Protocol
- Risk Analysis
- Description of the Device
- Monitoring Procedures
- Additional Records and Reports





# 5. Manufacturing Information

- FDA-Approved Device
  - Refer to its approved label
- FDA Approved Device – modified
  - Refer to its approved label & describe changes that were made
- Non-FDA Approved Device
  - Provide Letter of Authorization, or
  - Provide manufacturing information

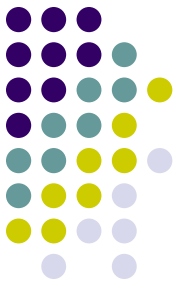




## 6. Investigators Agreement

- 21 CFR 812.43
- Statement of investigators commitment to:
  - Conduct the investigation according to the agreement
  - Supervise all testing
  - Ensure that requirements for obtaining of the IC are met
- CV of the investigator
- Statement of investigator's relevant experience
- Financial disclosure information





# IDE Submission

- Send original and 2 copies of your application
- Since Dec 2012 an electronic copy (eCopy) is required
- eCopy
  - An exact duplicate of the paper submission
  - If identical copy is not feasible, hard copy needs to cross-reference the location of information on eCopy
  - Cover letter must contain eCopy statement
  - Size of the submission is irrelevant

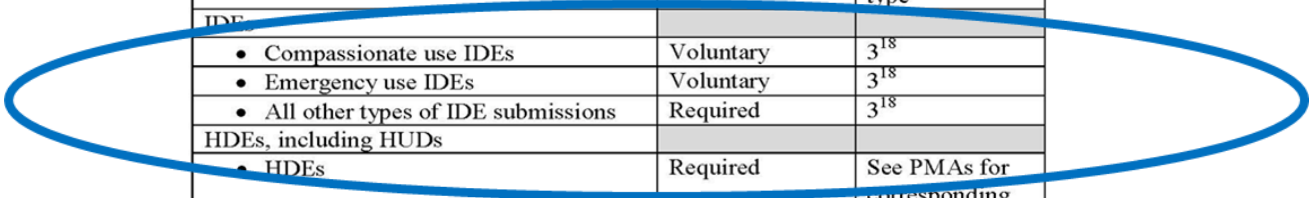




# IDE Submission

**Table 1 – Number of Copies for Submission**

Submission Type	Required or Voluntary eCopy	Total Number of Copies
510(k)s	Required	2 <sup>15</sup>
Third Party 510(k)s	Required	2 <sup>15</sup>
De Novos	Required	2
PMAs, including Transitional PMAs		
• Original PMAs	Required	6 <sup>16</sup>
• Panel-Track Supplements	Required	6 <sup>16</sup>
• All other PMA supplement types (e.g., 180-Day Supplements, Real-Time Supplements, 30-Day Notices, 135-Day Supplements)	Required	3 <sup>17</sup>
• PMA reports (annual reports and post-approval study reports)	Required	2
Modular PMAs	Required	3
PDPs	Required	See PMAs for corresponding type
IDEs		
• Compassionate use IDEs	Voluntary	3 <sup>18</sup>
• Emergency use IDEs	Voluntary	3 <sup>18</sup>
• All other types of IDE submissions	Required	3 <sup>18</sup>
HDEs, including HUDs		
• HDEs	Required	See PMAs for corresponding type <sup>19</sup>
• HUDs	Required	2 <sup>20</sup>
EUAs	Voluntary	3
INDs	Required	3 <sup>21</sup>
BLAs	Required	3
Pre-Submissions	Required	3
MAFs	Voluntary	2
513(g)s	Voluntary	3
CLIA X Files	Voluntary	3





# IDE Submission

- IDE should be sent to:

Food and Drug Administration

Center for Devices and Radiological Health (CDRH)

Document Mail Center

10903 New Hampshire Avenue

Silver Spring, Maryland 20993-0002







# FDA Review Process

- Sponsors are notified of the date that FDA received the original application
- IDE number is assigned (e.g., G130540)
- If eCopy is missing, you will be placed on “eCopy Hold”





# FDA Review Process

- Within 30 calendar days of the day the application has been received, FDA may:
  - Approve the investigation as proposed
  - Approve it with modifications
  - Disapprove it





# Reasons for Disapproval

- Risk associated with the study outweigh the benefits
- There are untrue statements in the applications
- Failure to respond to the request for additional information
- Inadequacy of monitoring, manufacturing, packaging, etc.



# Registering Trial on ClinicalTrial.gov



- “Applicable” clinical trials must be registered
  - A prospective study of health outcomes
  - Compares an intervention with a device against a control in human subject
  - The studied device is subject to 510(k), 515 or 520(m)
- Small feasibility study of a device, or a clinical trial to test prototype device when the primary outcome relates to feasibility and not to health outcomes is **NOT** an “applicable” study

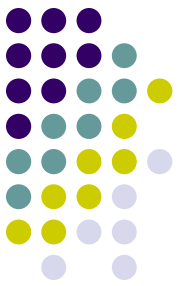


# Registering Trial on ClinicalTrial.gov



- ICMJE Policy
  - Study must be registered prior to enrollment of first subject
- PHS Act
  - No later than 21 days after enrollment of the first subject





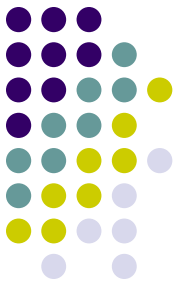
# IDE Modifications

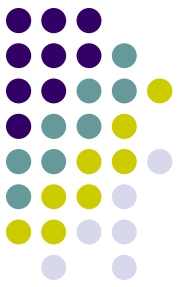
- Changes that require prior approval
  - 30-day review by FDA
- Changes that do not require prior approval
  - 5-day notice to FDA required before introducing change
- Changes submitted as a part of annual report
- Changes or Modifications During the Conduct of a Clinical Investigation
  - <http://tinyurl.com/42wvtny>



# IDE Maintenance

- Changes that require prior approval
  - 30-day review by FDA
  - Indication
  - Type or nature of study control
  - Primary end point
  - Statistical methods evaluation
  - Expanding the study (number of sites or subjects)
  - Significant design changes
  - Early termination





# IDE Maintenance

- Changes that require 5-day notice to FDA
  - A reply from FDA is usually not received
  - Emergency change
  - Non-significant design changes
  - Protocol changes
    - That do not effecting scientific soundness, rights/safety/welfare of subjects
    - Modification of inclusion/exclusion criteria to better define target population
    - Increasing frequency at which information is gathered
    - Modifying the secondary study endpoints.





# Supplements/Reports to FDA



- Unanticipated Adverse Device Effects
  - Within 10 working days
- Withdrawal of IRB approval
  - Within 5 working days
- Investigator List
  - Every 6 months
- Failure to Obtain Informed Consent
  - Within 5 working days
- Significant Risk Determination
  - Within 5 working day





# Supplements/Reports to FDA

- Final Report – SR study
  - Notification 30 working days from end of study
  - Report due within 6 months
  - Report provided to FDA and all reviewing the IRBs and participating investigators
- Final Report – NSR study
  - The sponsor shall submit a final report to all reviewing IRBs within 6 months after termination or completion
- 21 CFR 812.150



# Progress/Final Report



- Basic information
- Study Progress
  - Brief summary of the study progress
  - Number of investigators/investigational sites
  - Number of subjects enrolled
  - Number of devices shipped
  - Brief summary of results
  - Summary of anticipated and unanticipated adverse effects
  - Description of any deviations from the investigational plan



# Progress/Final Report



- Risk Analysis
  - Summary of any new adverse information (since the last progress report) that may affect the risk analysis
  - Reprints of any articles published from data collected from this study
  - New risk analysis, if necessary, based on new information and on study progress





# Progress/Final Report

- Other Changes
  - Summary of any changes in manufacturing practices and quality control
  - Summary of all changes in the investigational plan not required to be submitted in a supplemental application
- Marketing Application or Future Plans





# Submissions to the IDE

- Based on the type of information
  - Supplements
  - Reports
  - Amendments

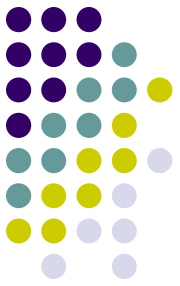




# Supplements

- Change in correspondent, manufacturer or sponsor
- Change in design or manufacturing
- Change in informed consent or protocol
- 5-day notices
- Expansion of study
- New study or protocol
- Extension of time to respond to FDA letter
- Notification of study suspended or resumed



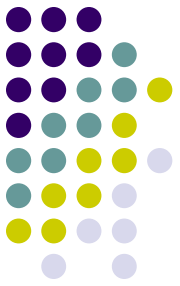


# Reports

- Adverse Effect
- Final, Study Completed
- Annual Progress
- Interim Progress
- Semiannual Investigator List
- Failure to Obtain Informed Consent
- Compassionate Use Follow-Up
- Emergency Use







# Amendments

- Response to Disapproval
- Response to Approval with Conditions
- Response to Refuse to Accept
- Response to Report of Deficiency
- Voluntary Withdrawal by Sponsor





# Terminating/Closing an IDE

- If IDE is still not yet approved – request a withdrawal
- If IDE is approved, but no subject enrolled – request a withdrawal
  - state why and account for all devices
- If subjects have been enrolled – you need to complete follow-up of enrolled subjects
- If study is completed – notify FDA within 30 days and send Final Report within 6 months





# In Vitro Diagnostics

- Definition of a medical device
  - An instrument, apparatus, implement, machine, contrivance, implant, **in vitro reagent**, or other similar or related article or component part or accessory that is **intended for use in the diagnosis** of disease or other condition, or in the cure, mitigation, treatment, or prevention of disease





# In Vitro Diagnostics

- IVDs include products used to collect specimens, or to prepare or examine specimens after they are removed from the human body.
  - Blood, spinal fluid, tissue samples, serum, urine
- IVDs include the entire process from specimen collection to results reporting
  - Specimen collection and transport
  - Specimen preparation
  - Specimen examination/analysis
  - Method of calculating/reporting result





# In Vitro Diagnostics

- Class I- Influenza IVD
- Class II- Blood glucose test
- Class III- HIV IVD, HPV IVD
- Risk classification based upon the harm if an incorrect result is produced by the IVD



# Diagnostic Device Studies



- Per 21 CFR 812.2 (c), a diagnostic device study is exempt of the IDE regulations when it:
  - Is noninvasive
  - Does not require an invasive sampling procedure that presents a significant risk
  - Does not by design or intention introduce energy into a subject
  - Is not used as a diagnostic procedure without confirmation of the diagnosis by another medically established diagnostic product or procedure

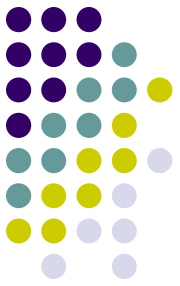




# Noninvasive Diagnostic Device

- “...A noninvasive device is one that does not, by design or intention:
  - penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra; or
  - enter the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or the vagina beyond the cervical os



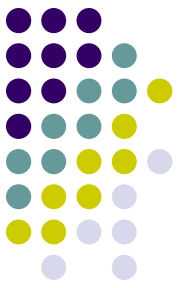


# Diagnostic Device Studies

- Per 21 CFR 812.2 (c), a diagnostic device study is IDE exempt when it:
  - Is noninvasive
  - Does not require an invasive sampling procedure that presents a significant risk







# Sampling Risk Assessment

- “...we recommend that you base your risk determination on the nature of the harm that may result from sampling. For example, FDA considers sampling techniques that require biopsy of a major organ, use of general anesthesia, or placement of a blood access line into an artery or large vein (subclavian, femoral, or iliac) to present a significant risk. . . .”



# Sampling Risk Assessment



- “...Blood sampling that involves simple venipuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for non-investigational purposes is also considered noninvasive . . . .”
- 21 CFR 812.3(k)





# Diagnostic Device Studies

- Per 21 CFR 812.2 (c), a diagnostic device study is IDE exempt when it:
  - Is not invasive
  - Does not require an invasive sampling procedure that presents a significant risk
  - Does not by design or intention introduce energy into a subject
  - Is not used as a diagnostic procedure without confirmation of the diagnosis by another medically established diagnostic product or procedure





# Confirmation of a Diagnostic Result

- “...test results ...should not influence patient treatment or clinical management decisions before the diagnosis is established by a medically established product or procedure“
- “...If an investigational test uses a new technology or represents a significant technological advance, established diagnostic products or procedures may not be adequate to confirm the diagnosis provided by the investigational IVD”
  - Therefore, this study can not be IDE exempt





# In Vitro Diagnostic Studies

- Two step process:
  - Does invasive sampling presents significant risk?
    - If yes, the study cannot be IDE exempt
  - If the study is not IDE exempt, then an SR/NSR determination of the whole study must be made



# Diagnostic Device Studies



- SR vs NSR determination
  - Significant risk device is one that is for a use of **substantial importance in diagnosing**, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and **presents a potential for serious risk** to the health, safety, welfare of a subject or otherwise presents a potential for serious risk to health, safety, or welfare of a subject (21 CFR 812.3 (m)).





# Diagnostic Device Studies

- FDA interprets “potential for serious risk” in relation to the harm that may result to the subject
- Misdiagnosis and/or error in treatment caused by an inaccurate test result would be considered SR if the result could be life-threatening or could result in permanent impairment or damage
  - Providing treatment or withholding treatment that has serious or life-threatening consequences



# In Vitro Diagnostic Device Studies



## Guidance for Industry and FDA Staff

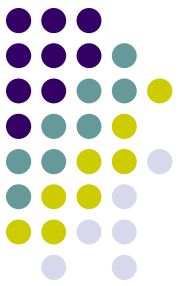
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### In Vitro Diagnostic (IVD) Device Studies -Frequently Asked Questions

<http://www.fda.gov/downloads/MedicalDevices/.../ucm071230.pdf>







# Other Types of Device Studies

- Emergency Use of Unapproved Medical Device
  - An IDE might or might not have been approved
  - Life-threatening situation that needs immediate treatment
  - There is no generally acceptable alternative for treating the patient
  - There is no time to use existing procedures to get FDA approval
  - Must be reported to FDA, IRB within 5 days



# Other Types of Device Studies



- Single Patient or Compassionate Use
  - Serious condition for which device is the only option
  - Patient does not meet inclusion, exclusion criteria
  - Prior approval of FDA and IRB is required
  - No clinical trial is available

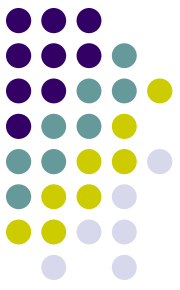


# Other Types of Device Studies



- Treatment IDE
  - 21 CFR 812.36
  - For serious or life-threatening condition
  - No alternative therapy
  - An appropriate level of safety and efficacy has been shown in clinical studies
  - Prior approval of FDA and IRB is required



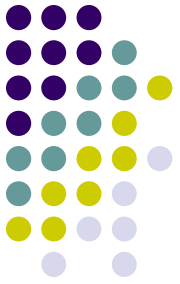


# Other Types of Device Studies

- Humanitarian Device Exemption
  - 21 CFR 814.100
  - A device that is intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 4,000 individuals in the US per year
  - HDE approval is similar to a PMA but is exempt from a proof of effectiveness requirement
  - With exception of emergency use, even if used per its approved label, the use of HUD requires IRB approval



# Contact Information



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