In Vitro Diagnostic Device Clinical Trials: Regulation and Review

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- Superior audit history with FDA—five consecutive audits with no findings
- 21 CFR Part 11 compliant electronic systems
- Compliant with FDA, OHRP and Health Canada requirements
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- Dedicated **daily expedited review** of qualifying minimal risk protocols
About Schulman IRB

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- **Expert oncology IRB members** experienced in all phases of oncology research
  - National IRB for **Cancer MoonShot 2020** initiative
- Customized services for **institutions**
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Danielle Macario, PhD
IRB Member, Schulman IRB
- With Schulman since 2013
- Serves as device specialist for IRB
- PhD in Biomedical Engineering specializing in Tissue Engineering
- Assisted medical device company in developing novel radiopaque polymeric stents as part of doctoral research
- Previously served with Johnson & Johnson Advanced Technologies group developing novel light therapy and microcurrent-based medical device studies
  - Ran clinical trials to improve outcomes in wound healing, itch, inflammation and pain
Overview

This webinar will delve into the various regulatory paths for devices, how that impacts the regulations they are subject to, and how they are reviewed by the IRB.

We will focus on in vitro diagnostics, particularly those exempt from most of the requirements of the IDE regulation.

CONTENT SUMMARY

LEARNING OBJECTIVES

Understand regulatory pathways for devices, specifically in vitro diagnostic tests

Understand considerations required for Laboratory Developed Tests

Learn what documentation to submit to the IRB depending upon the device category

TARGET AUDIENCE

- Research professionals involved in the development and conduct of device research
- Research professionals associated with organizations that sponsor device research
- Research professionals involved in submitting material for IRB review
- IRB members and support staff involved in review of device research
Agenda

- Regulatory pathways for device approval
- Understanding investigational device exemptions
- Documentation required for the IRB submission
- In vitro diagnostic products
- Laboratory developed tests
Regulatory Pathways for Device Approval
What Is a Medical Device?

Section 201(h) of the Food, Drugs and Cosmetics Act defines a medical device as any healthcare product that does not achieve its principal intended purposes by chemical action or by being metabolized.

- As simple as a tongue depressor or a thermometer
- As complex as robotic surgery devices

Is It a Device?
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/ucm051521.htm

Is It a Combination Product?
Contact FDA’s Office of Combination Product (OCP) by e-mail at: combination@fda.gov
Device Development Process

**Discovery & Concept**
Device concept to fit unmet need. Early design development based on predicate research, patents, etc. Too early for IRB review.

**Preclinical Prototype**
Building and testing the prototype. Controlled laboratory testing. Prototype not for human use, therefore no IRB review required.

**Approval Pathway**
Device pathway chosen based on its risk classification. Early feasibility studies through the IDE pathway. Establish device safety and effectiveness. IRB review and approval required.

**FDA Review**
File an application (depending on device class) to market the device. FDA may request additional studies to be performed in order to get device to market. IRB review required for all human subject research.

**Post-Market Safety Monitoring**
Address any new safety concerns once the device is on the market. Post-market safety studies may be required. IRB review required for additional safety and efficacy studies.
Device Development Process

- Non-clinical testing
  - Computational modeling
  - Bench testing
  - Animal studies

- Early clinical studies (first-in-man and feasibility)
  - Proof of concept
  - Device design iteration
  - Refine operator technique

- Trial to support market entry (pivotal trial)

- Post-marketing trials
  - Required postapproval studies
  - Additional trials to expand initial indications
IDE
• Investigational Device Exemptions
• Regulation 21 CFR 812

NSR
Abbrev 21 CFR 812

Exempt

510(k)
Premarketing submission to FDA demonstrating substantial equivalence to a marketed device

SR

HUD/HDE
• Humanitarian Use Device/ Humanitarian Device Exemption
• Exempt from effectiveness requirements of PMA

PMA
• Premarket Approval
• Most stringent device marketing application
• Safe and effective for intended use

De Novo
• Evaluation of Automatic Class III Designation
• Classification novel devices of low to moderate risk – after NSE (510[k])

Which process would be followed to gain approval for a device substantially equivalent to an existing device?

a) De Novo
b) 510(k)
c) PMA
d) HUD
Putting It Together

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b) 510(k)
c) PMA
d) HUD
Understanding Investigational Device Exemptions
IDE
• Investigational Device Exemptions
• Regulation 21 CFR 812

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Device Pathways

Investigational Device Exemption (IDE)

IDE allows investigational device to be used in a clinical study to collect safety and effectiveness data

- Supports 510(k) and PMA applications
- Exempts sponsor from certain provisions of Federal Food Drug and Cosmetic Act (FD&C Act)
- Requirements for informed consent, labeling, monitoring of the study, records/reporting
- Requires approval by IRB

21 CFR Part 812
Types of IDEs: Early Feasibility Study (EFS)

- Special type of feasibility study
- Generally <15 subjects
- Device may be early in development, before the device design has been finalized
- Approval of an early feasibility study IDE may be based on less nonclinical data
- Some nonclinical testing may be deferred
- Additional mitigations may be needed to protect subjects
- New EFS program within Center for Devices and Radiological Health (CDRH) designed to facilitate and support EFS research under an IDE
Types of IDEs: Feasibility Study

- Not intended to be the primary support for a marketing application
- May provide support for a future study or may be used to answer basic research questions
- Endpoints and sample size generally not statistically driven
- Often required by FDA prior to pivotal study to assess basic safety and potential for effectiveness
- Generally ~10-40 subjects but may be larger

FDA review is primarily focused on safety and whether the potential benefit or value of the data justifies risk
Types of IDEs: Pivotal Study

- Generally intended as primary clinical support for a marketing application
- Designed to demonstrate a “reasonable assurance of safety and effectiveness”
- Endpoints and sample size statistically driven
- Designed to assess both safety and effectiveness

- FDA review much more complex
  - Includes focus on whether study design is adequate to support future marketing application
IDE: What Is a Significant Risk Device?

- Intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject
- Purported or represented for supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject
- Used for substantial importance in diagnosing, curing, mitigating, or treating disease and presents a potential for serious risk to the health, safety, or welfare of a subject
- Otherwise presents a potential for serious risk to health, safety, or welfare of a subject

Examples: Dental lasers, embolization devices for urological use, and collagen and bone replacements
Abbreviated IDE: What Is a Non-Significant Risk Device?

- Does not meet the definition of a significant risk device
- Considered to have an approved IDE
- Abbreviated requirements at 21 CFR 812.2(b)

  Labeling, IRB approval, informed consent, monitoring, record keeping, reports, and prohibition against promotion

Examples: External monitors for insulin reactions, general biliary catheters, MRI within specified parameters
Abbreviated IDE: Non-Significant Risk vs. Minimal Risk

- **Minimal Risk:** term used in IRB regulations in part to identify certain studies that IRBs may approve through an expedited review procedure

- For a device study to be eligible for expedited review, it must meet category 1b:
  - Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; OR
  - (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling
  - Must also present no more than minimal risk to the subject

- A SR/NSR determination must be made at a convened IRB meeting
  
  21 CFR 56.110
IDE Exempt Studies

Certain studies are exempt from requirements of 21 CFR Part 812

This includes, but is not limited to:

- Consumer preference testing
- Testing a device modification
- Testing of two or more devices in commercial distribution if testing does not collect safety or effectiveness data, or put subjects at risk
- Studies of cleared medical device when used according to labeling
IDE Exempt Studies

- Includes many in vitro diagnostic (IVD) devices
- Under Section 812.2(c) of IDE regulations, studies exempt from IDE regulations include diagnostic devices if the testing:
  - Is noninvasive
  - Does not require invasive sampling procedure that presents significant risk
  - Does not by design or intention introduce energy into a subject; and
  - Is not used as a diagnostic procedure without confirmation by another medically established diagnostic product or procedure. \(21 \text{ CFR 812.2(c)(3)}\)
- No SR/NSR determination required by the IRB
- Must comply with labeling requirements under \(21 \text{ CFR 809.10(c)(2)}\)
Putting It Together

The following device study is eligible for expedited review:

a) Class II medical device being used within intended use
b) In vitro diagnostic device
c) Study with an FDA approved IDE
Putting It Together

The following device study is eligible for expedited review:

a) **Class II medical device being used within intended use**

b) in vitro diagnostic device

c) Study with an FDA approved IDE
Documentation Required for the IRB Submission
Sponsor’s Responsibilities for SR/NSR Studies

- Provide IRB with risk assessment and rationale used in making SR or NSR determination
- Any other information requested by the IRB, such as:
  - Description of device / device brochures
  - Reports of prior investigations
  - Proposed investigational plan
  - Subject selection criteria
- Inform IRB if FDA determined study to be NSR
- Sponsors may send their SR device study to IRB for review before IDE application is approved by FDA
  - Note: an SR device study may not begin until FDA approves the IDE
- Provide IDE number and/or copy of IDE approval letter to IRB when requested
- SR/NSR determination must be made at a convened IRB meeting
Sponsor’s Responsibilities for IDE Exempt Studies

- To assist IRB with its determination, the sponsor may provide the IRB with a brief rationale as to how the device meets the requirement under Section 812.2 (c)
- Any other information requested by the IRB, such as:
  - Description of device
  - Reports of prior investigations
  - Proposed investigational plan
  - Subject selection criteria

IDE Exempt determination can be made and study approved via expedited review provided the study is also minimal risk
A NSR device study is submitted to the IRB. What information should be provided?

a) Risk assessment and rationale for NSR determination
b) IDE approval from the FDA
c) NSR determination letter by FDA
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a) Risk assessment and rationale for NSR determination

b) IDE approval from the FDA

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In Vitro Diagnostic Products
What Is an In Vitro Diagnostic Product?

- Include products used to collect specimens, or to prepare or examine specimens after they are removed from the human body. 21 CFR 809.3
  - Specimens include: blood, serum, urine, spinal fluid, tissue samples

- IVDs are medical devices and may also be biological products subject to section 351 of the Public Health Service Act

- Subject to premarket and postmarket controls

- Subject to the Clinical Laboratory Improvement Amendments (CLIA '88) of 1988
When Does an IVD Study Involve Human Subjects?

**Human subject** means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control.

A subject may be either a healthy individual or a patient.

- Under FDA’s regulations governing the conduct of IVD device studies, the definition of subject includes individuals on whose specimens an investigational device is used [21 CFR 812.3(p)]
  - Therefore, an IVD study using human specimens involves human subjects
How Are IVDs Classified?

- FDA classifies IVD products into Class I, II, or III according to level of regulatory control necessary to assure safety and effectiveness.
- Classification of an IVD (or other medical device) determines the appropriate premarket process.

Class I
General Controls; Most exempt from premarket submission

Class II
General & Special Controls; Premarket Notification [510(k)]

Class III
General Controls; Require Premarket Application [PMA]

IVD: Regulatory Requirements

- Significant risk devices require an IDE approval
  - Examples: IVDs that require an invasive sampling technique that includes biopsy of a major organ, use of general anesthesia, or placement of a blood access line into an artery or large vein

- Non-significant risk devices: sponsor follows abbreviated requirements of 21 CFR 812.2(b)
  - Review and approval of the investigation by an IRB
  - Compliance with informed consent requirements

- Most IVDs are exempt from IDE requirements
When Is an IVD Exempt from Most Provisions of the IDE Regulation?

- Requirements for an IDE depend on level of risk the study presents to subjects
- Fits into one of the following 3 categories

1. The IVD
   - Is properly labeled in accordance with 21 CFR 809.10(c)
   - Is noninvasive
   - Does not require an invasive sampling procedure that presents significant risk
   - Does not by design or intention introduce energy into a subject and is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure
When Is an IVD Exempt from Most Provisions of the IDE Regulation?

2. Pre-amendments device other than a transitional device and is used or investigated according to the indications in the labeling at that time
   - I.e., a device that was in commercial distribution prior to the enactment of the 1976 Medical Device Amendments to the Act

3. Device, other than a transitional device, that has been found to be substantially equivalent to a pre-amendments device and is used or investigated according to the indications in the labeling reviewed by FDA in determining substantial equivalence
Some studies are exempt from most of 21 CFR Part 812 due to low risk to subjects.

However, following 21 CFR Part 812 is useful to sponsors and investigators of device studies to support PMA or other premarket submissions:
- Demonstrate product’s safety and effectiveness
- Protect study subjects

All studies that support applications to FDA are subject to 21 CFR 812.119(c) as well as to 21 CFR Parts 50 and 56.
Emergency Use of an IVD Device Outside of a Study Protocol

- A physician may use an investigational IVD device in an emergency situation if:
  - The patient has a serious disease or condition;
  - No generally accepted alternative diagnostic device or treatment for the condition is available; and
  - There is no time to use existing procedures to get FDA approval for the emergency use

- Physician should follow as many of the patient protection procedures as possible
  - Informed consent
  - Institutional clearance
  - Concurrence from IRB chairperson
  - Assessment from physician not participating in the study
  - Authorization from IDE sponsor (If existing IDE)
    ◊ OR authorization from device company (if no IDE)
IVD: Emergency Use Outside of a Study Protocol

- Prior approval of FDA not required
  - If IDE exists: submit supplemental IDE to report emergency use to FDA within 5 working days from time sponsor learns of use
  - If no IDE exists: report the emergency use to the sponsor and to CDRH or CBER, as appropriate
Labeling for IVD products is covered under 21 CFR 809.10

- Required labeling and package insert information for marketed and investigational products for distribution during clinical studies

FDA recommends a study design where the results support the proposed indications for use in package insert and labeling

Regulations that describe the basic content requirements by submission type include:

- Investigational Device Exemption (IDE) – 21 CFR 812.20
- Premarket Notification (510(k)) – 21 CFR 807.87
- Premarket Approval (PMA) – 21 CFR 814.20
- Humanitarian Device Exemption (HDE) – 21 CFR 814.104
An IVD is subject to the IDE regulations, depending on the level of risk the device poses.

a) True

b) False
An IVD is subject to the IDE regulations, depending up on the level of risk the device poses.

a) True

b) False
Laboratory Developed Tests
Laboratory Developed Tests

Medical Devices

In Vitro Diagnostic Devices

Laboratory Developed Tests
Laboratory Developed Tests

**Laboratory Developed Test (LDT):** in vitro diagnostic test that is designed, manufactured and used within a single laboratory

- Measures or detects a wide variety of analytes from a human body
  - I.e., proteins, glucose, cholesterol, or DNA
- Often same as the uses of FDA-cleared or approved in vitro diagnostic tests, but some labs may choose to offer their own test
- FDA does not consider diagnostic devices to be LDTs if they are designed or manufactured completely, or partly, outside of the laboratory that offers and uses them
Laboratory Developed Tests

- Premarket review for higher-risk LDTs i.e. those used to guide treatment decisions
- FDA plans to exercise enforcement discretion for low-risk LDTs and LDTs for rare diseases
FDA’s Regulatory Continuum
As Described in FDA’s 2013 MMA Guidance

- Not FDA Regulated
- Enforcement Discretion
- Full Compliance*
- Full Compliance 510(k)
- Full Compliance PMA

Not a Medical Device
Medical devices that FDA chooses not to regulate
Class I Low Risk
Class II Moderate Risk
Class III High Risk

*Unless otherwise exempt from certain requirements
Laboratory Developed Tests

Then…

- LDTs were originally relatively simple lab tests and available on a limited basis
- FDA did not enforce premarket review and other FDA requirements
- LDTs have evolved, become more pervasive

Now…

- Some LDTs are more complex, present higher risks (i.e. detection of risk for breast cancer and Alzheimer’s disease)
- FDA has identified problems with several high-risk LDTs
  - Claims that are not adequately supported with evidence
  - Lack of appropriate controls yielding erroneous results
  - Falsification of data
Laboratory Developed Tests

Health implications

- Due to these issues, there could be added risks to subjects
- People could initiate unnecessary treatment or delay or forego treatment altogether for a health condition, which could result in...
  - Illness or death
  - Patients being over- or undertreated for heart disease
  - Cancer patients being exposed to inappropriate therapies or not getting effective therapies
  - Incorrect diagnosis of autism
  - Unnecessary antibiotic treatments
  - Exposure to unnecessary, harmful treatments for certain diseases such as Lyme disease
Laboratory Developed Tests that fall under the enforcement discretion category include the following:

a) Class I devices
b) Low risk LDTs
c) LDTs for rare diseases
Putting It Together

Laboratory Developed Tests that fall under the enforcement discretion category include the following:

a) Class I devices  
b) Low risk LDTs  
c) LDTs for rare diseases
Conclusion

- Many of the regulatory paths to get a product to market involve the IDE regulations
- There are several categories under the IDE regulations: Significant Risk (highest risk), Non-Significant Risk, and Exempt (lowest risk)
- A study that requires a SR/NSR determination must be reviewed during a full board meeting at the IRB
- In vitro diagnostics are regulated based upon the risk level of the device
- Laboratory developed tests are a subset of IVDs
  - The potential health implications should be carefully considered for these studies
References

- How to Study and Market Your Device
  http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/

- NSR and SR Devices

- FDA Information Sheets
  http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials

- In Vitro Diagnostic Device Studies Guidance
In Vitro Diagnostic Device Clinical Trials: Regulation and Review

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