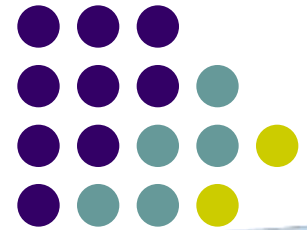


IDE Preparation and Maintenance: Best Practices Workshop

**PART 1: IDE Exemption Studies,
Abbreviated IDE and IDE**

**PART 2: IDE Maintenance and Additional
Device Studies**

Jelena P. Berglund, PhD, RAC
Associate Director, Regulatory Affairs

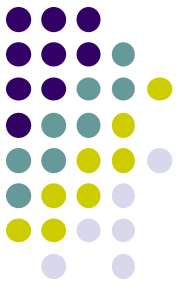


Duke Translational Medicine Institute



Duke Translational Medicine Institute
DUKE UNIVERSITY MEDICAL CENTER

Regulatory Affairs Office



Front Row (L-R): Bruce Burnett, PhD, RAC; Audrey Perry, Erin O'Reilly, PhD, RAC; Amanda Parrish, PhD, RAC

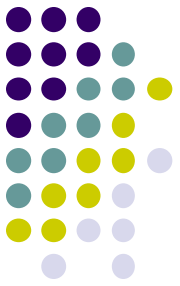
Back Row (L-R): Preeti Chugha, PhD, PMP; Jelena Petrovic Berglund, PhD, RAC; Erika Segear Johnson, PhD



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Our Website: Templates and Instructions



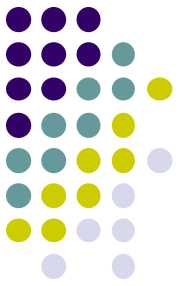
- Best Practices Templates/Instructions

<http://tinyurl.com/axwxkmv>

- Recorded Webcasts

<http://tinyurl.com/m269l7n>

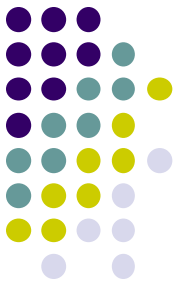
PART 1: IDE Exemption Studies, Abbreviated IDE and IDE



- **Background**
- **Clinical Investigations of a Medical Device**
- **IDE Exemptions**
- **SR/NSR Determination and Abbreviated IDE**
- **Pre-Submission Meetings with the FDA**
- **IDE Preparation and Submission**

What is a Medical Device?

513(a)(1) for the FD&C Act



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 it's primary intended purposes through physical action and NOT chemical or metabolic action**



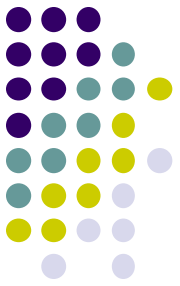
What is a Medical Device?



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Medical Device Regulation

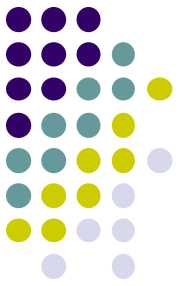


Medical Device Amendments in 1976

- Prior to 1976, investigational devices were either not reviewed or reviewed as drugs
- Established device classifications based on risk
- Established the Investigational Device Exemption (IDE)



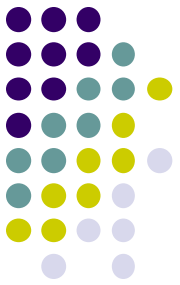
Medical Device Classification



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



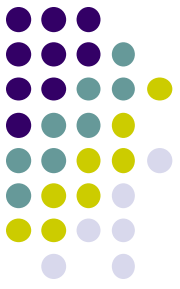
Medical Device Classification



- **Class I** - *e.g. dental floss, medical scissors, dental syringe*
- **Class II** – *powered wheel chair, MRI, clinical mercury thermometer*
- **Class III** - *e.g. external defibrillator, replacement heart valves*



Medical Device Classification



- Devices are classified related to the: **medical specialties**: 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

[876](#) Gastroenterology and Urology

[878](#) General and Plastic Surgery

[880](#) General Hospital and Personal Use

[882](#) Neurology

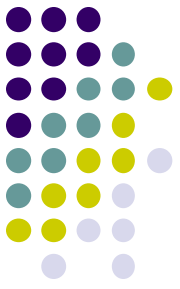
[884](#) Obstetrical and Gynecological

[886](#) Ophthalmic

[888](#) Orthopedic

[890](#) Physical Medicine

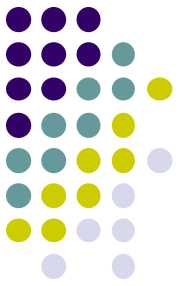
[892](#) Radiology



Medical Device Classification

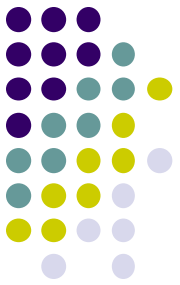
- Devices are classified based on the **time** of their marketing
 - **pre-Amendments** device – marketed prior to 1976
 - **post-Amendments** device - marketed after 1976
 - **Transitional devices** - those regulated as drugs prior to the '76 Amendments, but subsequently as devices

Summary of Devices Classifications



- Based on the **risk** (Class I, II & III) NSR & SR
- Based on **medical specialties** (into 16 groups)
- Based on the **time** (pre- , post-amendment, transitional)

Commercialization Options



- **Exempt** – most Class I and a few Class II devices are exempt from the 510(k) regulations
- **510(k)** - device is at least as safe and effective, or substantially equivalent to, a legally marketed device (predicate) that is not subjected to a PMA
 - 90 day FDA review <http://tinyurl.com/qeh79qn>
- **PMA** - premarket approval is required for all Class III devices. Focus on scientific and regulatory review of safety and effectiveness
 - 180 day FDA review

Medical Device Classification

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm>



Product Classification

[FDA Home](#) [Medical Devices](#) [Databases](#)



This database includes:

- a list of all medical devices with their associated classifications, product codes, FDA premarket review organizations, and other regulatory information.

[Learn More...](#)

Search Database

[Help](#) [Download Files](#)

Device

Product Code

Review Panel

Regulation Number

SubmissionType

Third Party Eligible

Device Class

[Go to Quick Search](#)

[Clear Form](#)

Other Databases

- [510\(k\)s](#)
- [De Novo](#)
- [Medical Device Reports \(MAUDE\)](#)
- [CDRH FOIA Electronic Reading Room](#)
- [CFR Title 21](#)
- [CLIA](#)
- [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](#)

Need information about classifying your device?

[Device Classification](#)

Page Last Updated: 10/06/2014

Note: If you need help accessing information in different file formats, see [Instructions for Downloading Viewers and Players](#).

Example

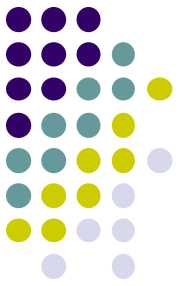


Product Classification

[FDA Home](#) [Medical Devices](#) [Databases](#)

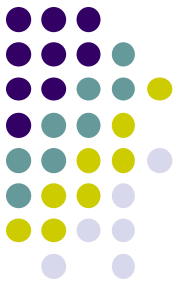
New Search		Back To Search Results
Device	Maggots, Medical	
Definition	Phaenicia sericacta (blow fly) larvae are harvested and provided disinfected for use in debriding non-healing necrotic skin and soft tissue wounds, including pressure ulcers, venous stasis ulcers, neuropathic foot ulcers, and non-healing traumatic or post surgical wounds.	
Review Panel	General & Plastic Surgery	
Product Code	NQK	
Premarket Review	Office of Device Evaluation (ODE) Division of Surgical Devices (DSD) General Surgery Devices Branch One - Light Based/Laser (GSDB1)	
Unclassified Reason	Pre-Amendment	
Submission Type	510(k)	
Device Class	Unclassified	
Total Product Life Cycle (TPLC)	TPLC Product Code Report	
GMP Exempt?	No	
Third Party Review	Not Third Party Eligible	

PART 1: IDE Exemption Studies, Abbreviated IDE and IDE



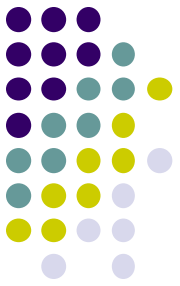
- Background
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Clinical Study of an Investigational Device

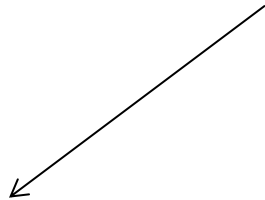


- If the objective of the study is to assess the **safety and/or effectiveness** of a device, the study is subject to 21 CFR 812.
- Studies using devices as **“tools”**
 - This is in contrast with the practice of medicine – a physician can use a device (or drug) without regulatory approval
 - Only when used as a part of clinical investigation, a device might be subject to 21 CFR812

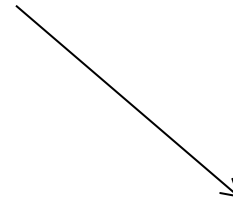
Clinical Investigation of Medical Device



All Clinical Investigations of Medical Device:



be **exempt** from the IDE regulations (21 CFR 812.2 (c))

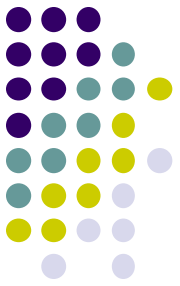


have an IDE

a) **abbreviated IDE** (21 CFR 812.2 (b))

b) **IDE** (21 CFR 812.20)

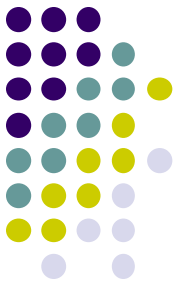
PART 1: IDE Exemption Studies, Abbreviated IDE and IDE



- Background
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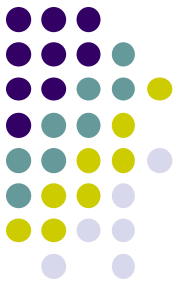
Investigations **Exempt** from the IDE Regulations



- A legally marketed device when 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
- A device intended solely for veterinary use
- A device for research on or with laboratory animals
- A custom device (21 CFR 812.3(b)) (<http://tinyurl.com/lbx19k8>)



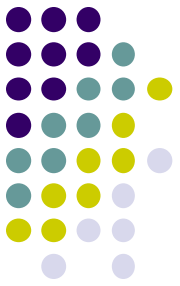
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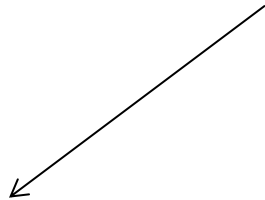
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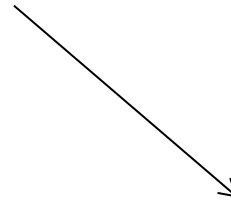
Clinical Investigation of Medical Device



All clinical investigation of device must:



be **exempt** from the IDE regulations (21 CFR 812.2 (c))

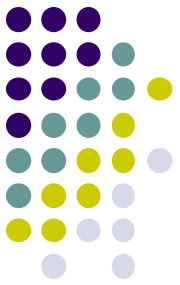


have an IDE

a) **abbreviated IDE** (21 CFR 812.2 (b))

b) **IDE** (21 CFR 812.20)

Difference between an abbreviated IDE and IDE?



- Who is overseeing the study:

IRB (*abbreviated IDE*)

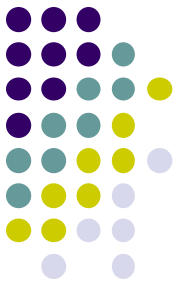
- **Non-significant risk** (NSR) device
- Not a banned device (21CFR 895.101)
- Must have informed consent

FDA and IRB

- **Significant risk** (SR) device
- Investigation exempt from the informed consent
- FDA notifies the sponsor that IDE application is required

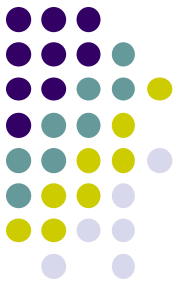
What are Significant Risk Devices?

21 CFR 812.3 (m)



- Significant Risk Device is investigational 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

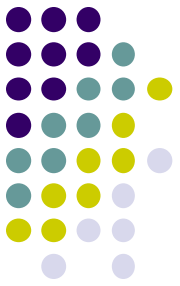
**Significant Risk and Nonsignificant
Risk Medical Device Studies**

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



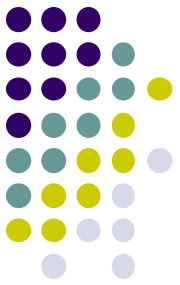
If the Investigational Study is NSR

(21 CFR 812.2 (b))



Trial can be run under an abbreviated IDE...

Obtaining an IRB Approval

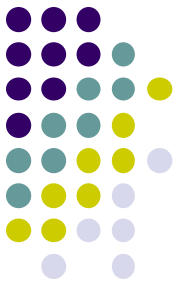


- Sponsor makes initial significant or non-significant risk study determination
- Submit to the IRB required documents:
 - description of the device
 - explanation why you believe that the device is NSR device
 - report of prior investigation
 - proposed investigational plan
 - other
- If IRB agrees with sponsor, study can be conducted under the IRB oversight only



Abbreviated IDE

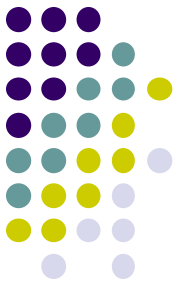
(21 CFR 812.2 (b))



- 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

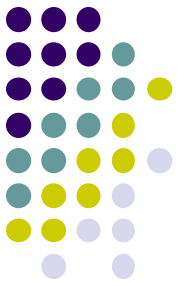


If IRB Disagrees with the NSR Determination



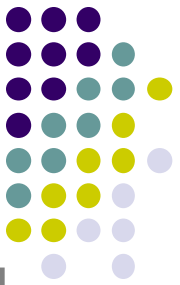
- **The Agency needs to make SR/NSR determination.**
- **The decision is binding**

PART 1: IDE Exemption Studies, Abbreviated IDE and IDE



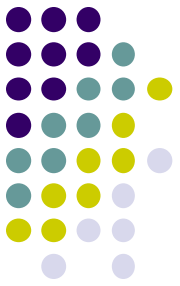
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Q-Sub Program: Requests for FDA Feedback



Q-Sub Type	Meeting as Method of Feedback?	Timeframe for Meeting/Teleconference (from receipt of submission)
Pre-Submission	Upon Request	75-90 days
Informational Meeting	Yes	90 days
Study Risk Determination	No	N/A
Agreement Meeting	Yes	30 days or within time frame agreed to with sponsor
Determination Meeting	Yes	Date for meeting agreed upon within 30 days of request
Submission Issue Meeting	Yes	21 days
Day 100 Meeting	Yes	100 days (from PMA filing date)

Q-Sub Program: Pre-Submissions



- A pre-submission is defined as 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.

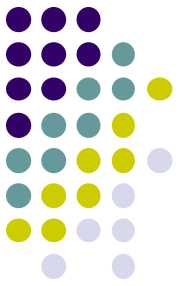
Guidance: <http://tinyurl.com/kvbf54z>

Q-Sub Program: Pre-Submissions



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

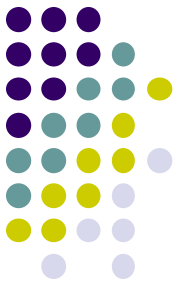
Q-Sub Program: Pre-Submissions



- Similar to pre-IND for drugs: 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 meeting schedule in drug development).

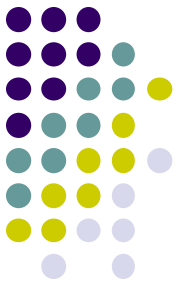


Q-Sub Program: Study Risk Determination



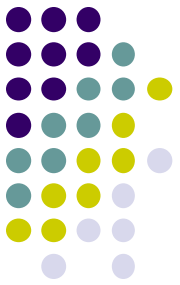
- **Informal: Email/Call**
- **Formal: Pre-Submission Study Determination Request**
 - Include device information and clinical protocol
 - Recommend cover letter and highlight nature of request
 - Response usually within 60 days (binding determination); no Q-Sub timing
- **Formal: Submit full IDE**
 - Response within 30 days



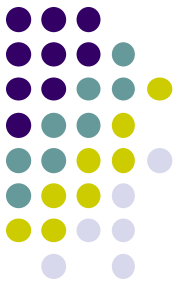


Case Studies

Scenario 1



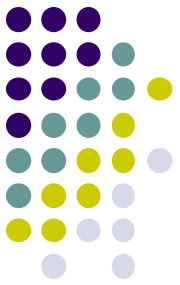
- The objective of the proposed study is to assess safety and efficacy of a CancerSTOP drug in combination with various anti-androgens on prostate cancer. Cancer progression is assessed with the use of a CT scan.
- Is this a Drug study?
- Is this a Device study?
- Is this both drug and device study?



Scenario 2

- An investigator is planning on studying the safety and effectiveness of the FDA-approved device (SLIM). The device is a PMA-approved as an implantable gastric bypass. The study is assessing the safety and efficacy of that device in combination with specific gastric surgical procedure that will be performed in the same time.
- Q 1: Is this a device study?
- Q 2: Can this study be IDE exempt?

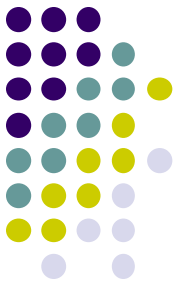
Investigations **Exempt** from the IDE Regulations



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- A device intended solely for veterinary use
- A device for research on or with laboratory animals
- A custom device (21 CFR 812.3(b)) (<http://tinyurl.com/lbxl9k8>)

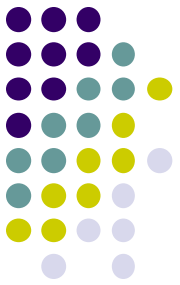


Scenario 2



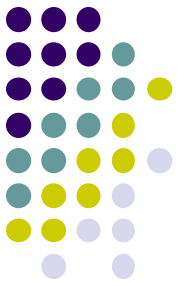
- Q3: In your opinion is this a SR or NSR Study?
 - Not used per its label
 - It is implant approved via PMA
 - Potentially prolonged time of surgery
 - Potentially increased risks associated with the device itself
 - Study required an IDE

Scenario 3



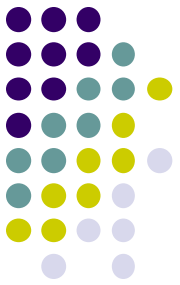
- An investigator is running a multi-center trial. In 3 out of 4 participating institutions, the reviewing IRBs agreed with the investigator that the device trial is a NSR study. The 4th IRB sees it as SR device study. What should investigator do?
 1. ignore the 4th IRB, since 3 others agreed
 2. do not use the 4th site
 3. ask FDA for the opinion by sending an IDE application
 4. ask the FDA by giving them a call

PART 1: IDE Exemption Studies, Abbreviated IDE and IDE



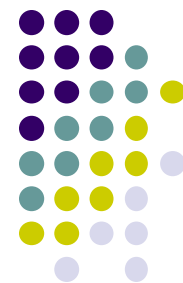
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- **IDE Preparation and Submission**

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

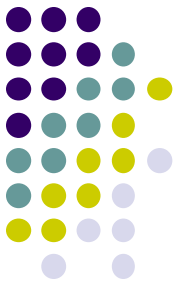
1. Cover Sheet – Form 3514



- used **voluntarily**
- same form is used for IDE, 510(k), PMA, meetings, 513(g) etc.
- captures the following information:
 - **original submission**, amendment, report or supplement
 - **device information (name, intended use)**
 - sponsor and manufacturer contact info
 - any previous discussion with the FDA

IDE Content

21 CFR 812.20 (b)



1. Cover Sheet – form 3514
2. Name and Address of the Sponsor
3. Report of Prior Investigations

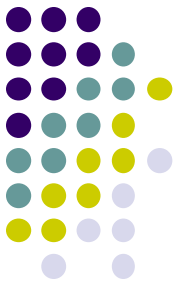


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Transforming Medicine

3. Report of Prior Investigation

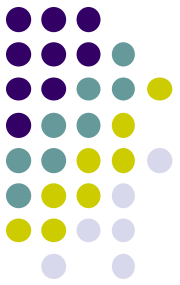
(21 CFR 812.27)



- General
 - prior clinical, animal and laboratory testing
- Specific
 - bibliography of all publications
 - summary of all unpublished information
 - if laboratory studies are referenced, statement whether such a studies have been done according to the GLP

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

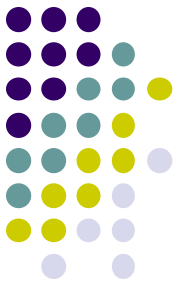


DTMI

Transforming Medicine

4. Investigational Plan

(21 CFR 812.25)

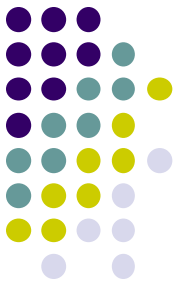


- Purpose – name and intended use
- Protocol
- Risk Analysis
- Description of the Device
- Monitoring Procedures
- Additional Records and Reports



IDE Content

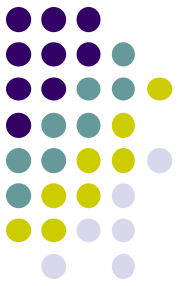
21 CFR 812.20 (b)



1. Cover Sheet – form 3514
2. Name and Address of the Sponsor
3. Report of Prior Investigations
4. Investigational Plan
5. Manufacturing Information

5. Manufacturing Information

21 CFR 812.20(b)(3)

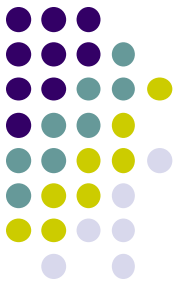


- FDA-Approved Device – off label and/or modified
- Non-FDA Approved Device – from a company
- Non-FDA Approved Device – you control manufacturing



5. Manufacturing Information

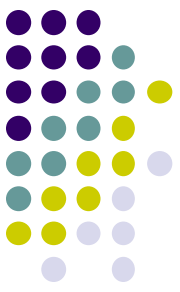
21 CFR 812.20(b)(3)



- Refer to its approved label
- Refer to its approved label & describe changes that you make
- Refer to Letter of Authorization (LoA)



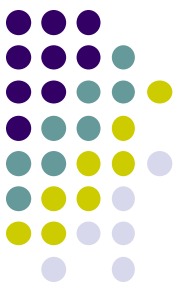
What is a Letter of Authorization?



- This is a letter from a sponsor (company) to their IDE (or IND or MF) stating that confidential information from their submission can be used in support of your submission
- Thus, the FDA has “permission” to reference the named materials in support of your IDE
- Get copies of the letters to include in your submission

5. Manufacturing Information

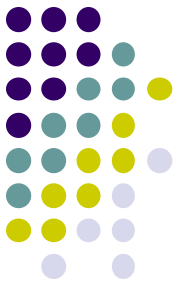
21 CFR 812.20(b)(3)



- Methods, facilities, and controls for:
 - Manufacturing
 - Packaging
 - Storage
 - Installation

IDE Content

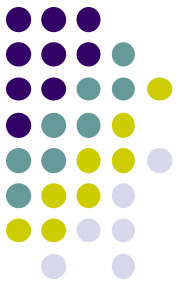
21 CFR 812.20 (b)



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

6. Investigators Agreement

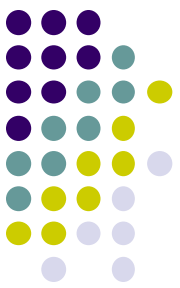
(21 CFR 812.43)



- Who is the investigator?
 - Investigator is an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the investigational device is administered, dispensed to, or used
 - In the event of an investigation being conducted by a team of individuals, "investigator" refers to the responsible leader of that team

6. Investigators Agreement

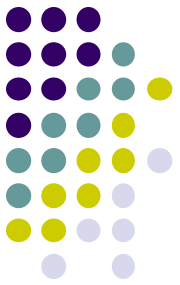
(21 CFR 812.43)



- CV of the investigator
- Statement of investigator's relevant experience
- If investigator was involved in the investigation that got terminated, explain the circumstances
- Financial disclosure information
- 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

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

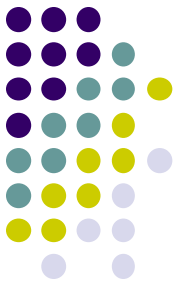


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Transforming Medicine

IDE Content

21 CFR 812.20 (b)



- 8. IRB Information
- 9. Name and Address of Investigators
Institution
- 10. Financial Claims
- 11. Environmental Assessment
- 12. Labeling
- 13. Informed Consent
- 14. Additional Information



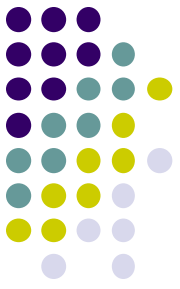
DTMI

Transforming Medicine

IDE Content (21 CFR 812.20 (b))



1. Cover Sheet – form 3514
 2. Name and Address of the Sponsor
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 4. Investigational Plan
 5. Manufacturing Information
 6. Investigators Agreement
 7. Investigators Certification
 8. IRB Information
 9. Name and Address of Investigators Institution
 10. Financial Claims
 11. Environmental Assessment
 12. Labeling
 13. Informed Consent
 14. Additional Information
- <http://tinyurl.com/axwxkmv>



Original IDE Submission

- Send 3 copies of your application
- Since Dec 2012 eCopy necessary!!
 - An exact duplicate of the paper submission
 - It can be CD, DVD, or flash drive
 - If identical copy is not feasible, hard copy needs to have a placeholder cross-referencing the location of certain info on eCopy
 - Cover letter must contain eCopy statement
 - Size of the submission is irrelevant
 - Use Adobe Acrobat 11 and below
 - No security settings
 - 50MB or smaller in size

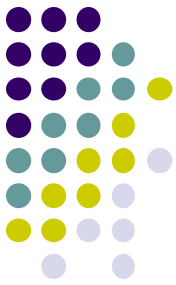


Table 1 – Number of Copies for Submission

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

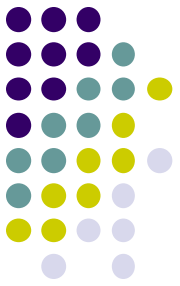
¹⁵ See 21 CFR 807.90(a)(3)(c).

¹⁶ See 21 CFR 814.20(b)(2).

¹⁷ See 21 CFR 814.39(c).

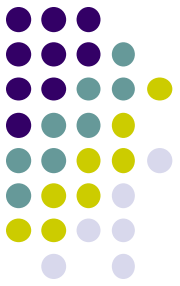
¹⁸ See 21 CFR 812.20(a)(3).

Creating an eCopy



- Non-Volume Based eCopy
 - 001_G010101_Annual report 2014.pdf
- Volume Based eCopy
 - VOL_001_Cover letter
 - VOL_002_Report of Prior Investigations

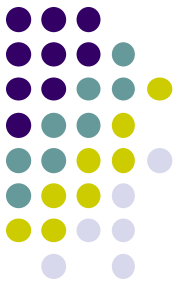
<http://tinyurl.com/99jtgle>



IDE Submission

IDE should be sent to:

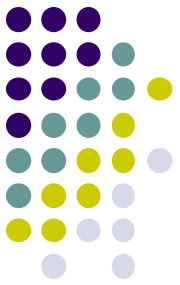
Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002



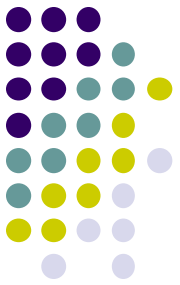
FDA Review Process

- Sponsors are notified of the date that FDA received the original application
- IDE number is assigned (e.g., G096000)
 - If eCopy is missing, you will be placed on “eCopy Hold”
 - Send eCopy only with the appropriate statement

FDA Review Process



- Within 30 calendar days of the day the application has been received, FDA may grant:
 - **IDE Approval**
 - **IDE Approval with Conditions**
 - **Staged Approval (with Conditions)**
 - **IDE Disapproval**
- An IDE application is considered approved 30 days after it has been received by FDA
 - <http://tinyurl.com/lxrmd9u>



Let's Take a Break!



The plan to increase productivity by canceling coffee breaks flopped.



IDE Preparation and Maintenance: Best Practices Workshop

**PART 1: IDE Exemption Studies,
Abbreviated IDE and IDE**

**PART 2: IDE Maintenance and Additional
Device Studies**

Jelena P. Berglund, PhD, RAC
Associate Director, Regulatory Affairs

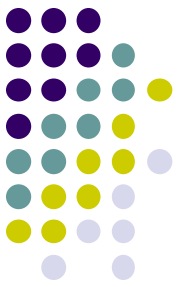


Duke Translational Medicine Institute



Duke Translational Medicine Institute
DUKE UNIVERSITY MEDICAL CENTER

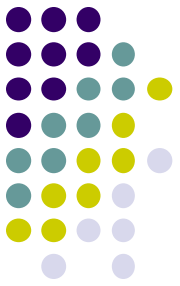
PART 2: IDE Maintenance and Additional Device Studies



- IDE Maintenance
 - *In Vitro* Diagnostic (IVD) Devices
 - IVD Multivariate Index Assay (IVDMIA)
- Additional Type of Device Studies
- Case Studies



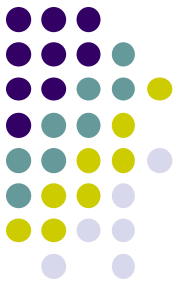
Once you have an active IDE...



- Make sure that you also have IRB approval(s) in place

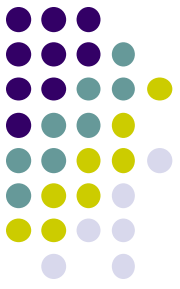


Registering Trial on ClinicalTrial.gov

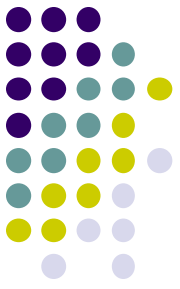


- Introduced by FDAAA in 2007
- **Do not** need to send a 3674 form to the FDA with your IDE submission
- **Do** need to register “applicable trial” on ClinicalTrial.gov

What is the “Applicable Clinical Trial”?



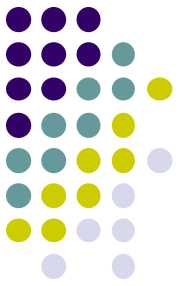
- Defined in the 402(j) of the PHS Act
 - prospective study of health outcomes
 - compares an intervention with a device against a control in human subject
 - the studied device is subject to 510(k), 515 or 520(m)
 - its **OTHER** then a small clinical trial to determine a **feasibility** of device, or a clinical trial to test prototype device when the primary outcome relates to feasibility and not to health outcomes



Deadline(s) for Registering Trials

- 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
-
- <http://tinyurl.com/6pog3s4>
 - <http://tinyurl.com/n527eab>
 - <http://tinyurl.com/8xtnc7r>

Requirements for IDE Modifications



- Changes that require prior approval (30-day reply from FDA)
- Changes that DO NOT require prior approval (require 5-day notice to FDA)
- Changes submitted as a part of annual report
 - <http://tinyurl.com/42wvtny>

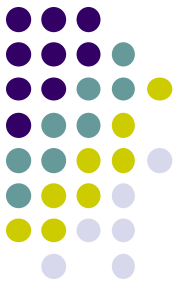
IDE Modifications



- Changes that **require prior approval** (30-day reply from 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



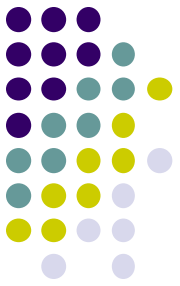
IDE Maintenance



Changes that require **5-day notice** to FDA (do not usually receive reply from FDA):

- Emergency change
- Non-significant design changes
- Some protocol changes
 - Not effecting scientific soundness, rights/safety/welfare of subjects
 - Modification of incl/excl criteria to better define target population
 - Increasing frequency at which information is gathered
 - Modifying the secondary study endpoints.

IDE Maintenance



- Changes that notice to FDA in the annual report include minor changes in the following areas (do not usually receive reply from FDA):
 - Monitoring procedures
 - Labeling
 - Informed Consent Materials
 - IRB Information

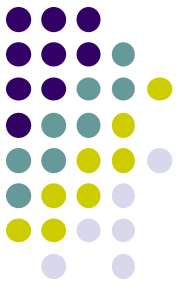
Supplements/Reports to FDA



	FDA
Unanticipated Adverse Device Effects	10 working days
Withdrawal from FDA/IRB approval	5 working days
Investigator List	Every 6 months
Progress Report (Annual Report)	At least yearly
Deviation from Investigational Plan	5 working days or pre-approval
Failure to Obtain Informed Consent	5 working days
Recall and Device Disposition	30 working days
Significant Risk Determination	5 working days
Final Report	30 working days- notification 6 months- report

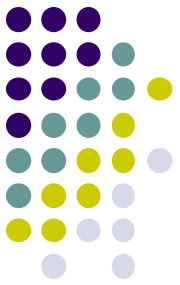
21 CFR 812.150

IDE Maintenance - UADEs



- Unanticipated Adverse Device Effect - Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (21 CFR 812.3 (s)).
- Conduct an evaluation of the UADE and report to the FDA within 10 working days.

Progress/Final Report



1. Basic information
2. Study Progress
 - Brief summary of the study progress
 - Number of investigators/investigational sites
 - Number of subjects enrolled
 - Number of devices shipped
 - **Disposition of all device shipped**
 - Brief summary of results
 - Summary of anticipated and unanticipated adverse effects
 - Description of any deviations from the investigational plan (since last progress report)



Progress/Final Report



3. Risk Analysis

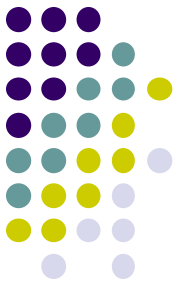
- Summary of any new adverse information (since the last progress report) that may affect the risk analysis
- Reprints of any articles published from data collected from this study
- New risk analysis, if necessary, based on new information and on study progress

4. 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

5. Marketing Application or Future Plans

Submissions to the IDE Based on Type of Information



- Supplements
- Reports
- Amendments
- <http://tinyurl.com/lxrmd9u>

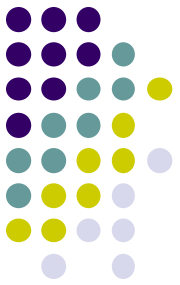
Supplements



- Approval for change (prior-approval, 5-day notice)
- Request approval for a new study under the same IDE
- Request study expansion (new sites, more patients)
- Request approval to terminate enrollment/study
- Notify FDA if the study been suspended
- Request approval for the compassionate use
- Request the extension of time to respond to the FDA

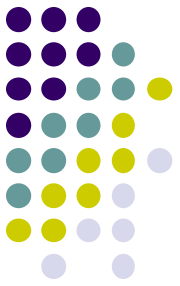
The FDA will usually reply. Reply is similar to the Original IDE submission

Reports



- Provide biannual investigator/IRB information
- Annual reports
- Failure to obtain ICF
- Notify the FDA of the Emergency Use
- Report the unanticipated adverse device effect
- Report completion of enrolment/study
- Provide final IDE report

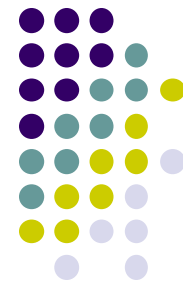
The FDA will reply within the 30 days IF they have any comments



Amendments

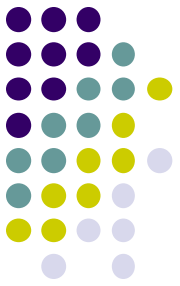
- Any repose to deficiency letter is an amendment. Amendment may be submitted to each of the 3 parent document types:
- Original IDE submission
- IDE Supplement
- IDE Report

Terminating/Closing an IDE



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

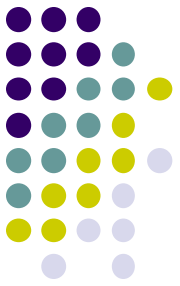
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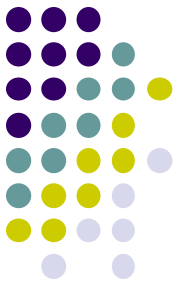
In Vitro Diagnostics – Why are They Devices?



It is 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
- Is *intended to affect the structure or any function of the body*
- *And does not achieve its intended purpose through chemical action or being metabolized for the achievement of its primary purpose*

In Vitro Diagnostic Device Studies

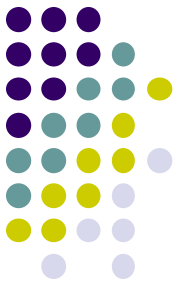


An IVD device is often different from other devices because most other devices function ON or IN a patient.

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

In Vitro Diagnostic Device Studies

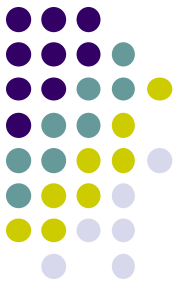


The FDA considers the IVD to be the entire process from specimen collection to results reporting.

- Specimen collection and transport
- Specimen preparation
- Specimen examination/analysis
- Method of calculating/reporting result



In Vitro Diagnostic Device Studies



Examples:

- Class I- Influenza IVD
- Class II- Blood glucose test
- Class III- HIV IVD, HPV IVD

Clinical Investigation of Medical Diagnostic Device



All clinical investigation of device must:

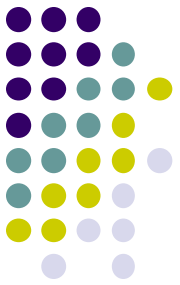
be **exempt** from the IDE regulations (21 CFR 812.2 (c))

have an approved IDE

a) **abbreviated IDE** (21 CFR 812.2 (b))

b) **IDE** (21 CFR 812.20)

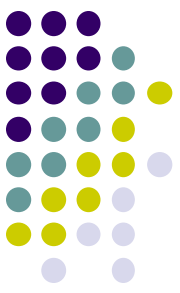
Investigations **Exempt** from the IDE Regulations



- A legally marketed device when 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
- A device intended solely for veterinary use
- A device for research on or with laboratory animals
- A custom device (21 CFR 812.3(b)) (<http://tinyurl.com/lbxl9k8>)



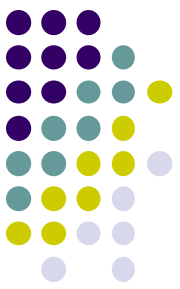
Diagnostic & *In Vitro* Diagnostic Device Studies



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**
- 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

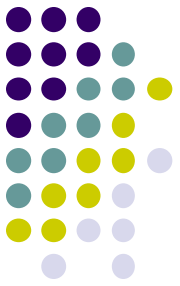
When Diagnostic Device is Noninvasive



“...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.

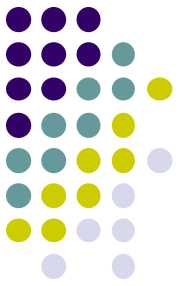
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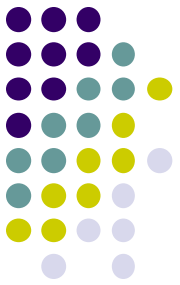
Invasive Sampling Procedure That Does Not Present a Significant Risk



“...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.”



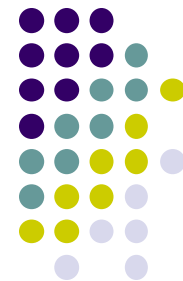
Invasive Sampling Procedure That Does Not Present a Significant Risk



“...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 noninvestigational purposes is also considered noninvasive (21 CFR 812.3(k)).”

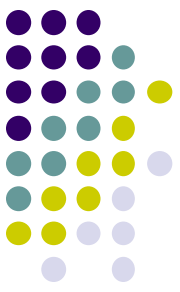


Diagnostic & *In Vitro* Diagnostic Device Studies



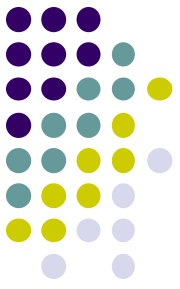
- Two step process:
 - Does invasive sampling presents SR
(if so, study cannot be IDE exempt)
 - If study is not IDE exempt, then
SR/NSR determination of the whole study
needs to be made

Diagnostic & *In Vitro* Diagnostic Device Studies



Per 21 CFR 812.2 (c), a diagnostic device study is **IDE exempt** when it:

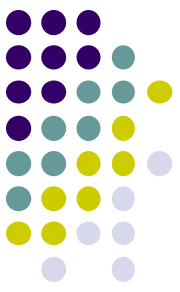
- Is **not invasive**
- Does **not** require an **invasive sampling** procedure that presents a **significant risk**
- Does **not** by design or intention **introduce energy** into a subject
- Is **not** used as a diagnostic procedure **without confirmation** of the diagnosis by another medically established diagnostic product or procedure



Confirmation of Diagnostic (or IVD) Results

- *“...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, the study can not be IDE exempt*

Diagnostic & *In Vitro* Diagnostic Device Studies

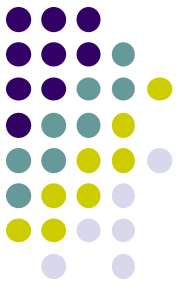


Per 21 CFR 812.2 (c), a diagnostic device study is **IDE exempt** when it:

- Is **noninvasive**
- Does **not** require an **invasive sampling** procedure that presents a **significant risk**
- 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



Clinical Investigation of Medical Diagnostic Device



All clinical investigation of device must:

be **exempt** from the IDE regulations (21 CFR 812.2 (c))

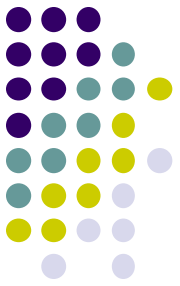
have an approved IDE

a) **abbreviated IDE** (21 CFR 812.2 (b))

b) **IDE** (21 CFR 812.20)



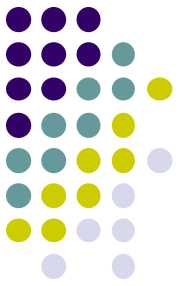
SR vs NSR Diagnostic Device Studies



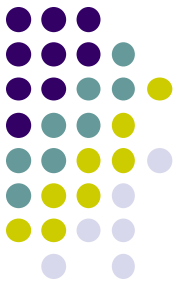
Significant risk IVD study is one that is for a use of **substantial importance in diagnosing**, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a **potential for serious risk** to the health, safety, welfare of a subject or otherwise presents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



SR vs NSR 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 inaccurate test results would be considered SR if the result could be life-threatening or could result in permanent impairment or damage.
 - ex. subject was given an unnecessary treatment or delay in treatment for serious or life-threatening conditions

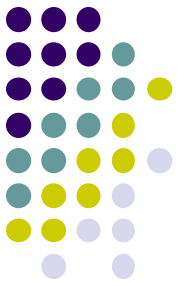


Guidance for Industry and FDA Staff

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

Guidance: <http://tinyurl.com/4b4vlmj>

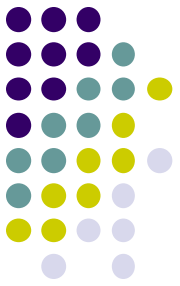
In Vitro Diagnostic Device Study Considerations



- Biorepositories
- When does IVD development begin?



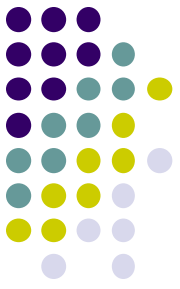
PART 2: IDE Maintenance and Additional Device Studies



- IDE Maintenance
- *In Vitro* Diagnostic (IVD) Devices
- **IVD Multivariate Index Assay (IVDMIA)**
- Additional Type of Device Studies
- Case Studies



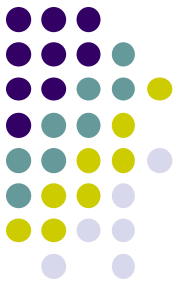
In Vitro Diagnostic Multivariate Index Assays (IVDMIA)



- IVDMIA is a device that:
 - 1) *“Combines the values of multiple variables using an interpretation function to yield a single, patient-specific result (e.g. a “classification”, “score”, “index” etc.), that is intended for use in the diagnosis of disease or other condition, or in the cure, mitigation, treatment or prevention”*
 - 2) *“Provides a result whose derivation is non-transparent and cannot be independently derived or verified by the end user”*

<http://tinyurl.com/mgmnrt7>

In Vitro Diagnostic Multivariate Index Assays (IVDMIA)



Examples of what the FDA considers IVDMIA:

- A device that integrates quantitative results from multiple immunoassays to obtain a qualitative “score” that predicts a person’s risk of developing a disease or condition.
- A device that integrates a patient’s age, sex, and genotype of multiple genes to predict risk of or diagnose a disease or condition.



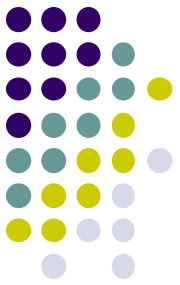
Examples of what the FDA DOES NOT consider

IVDMIA:

- *“Common clinical calculations (e.g., creatinine clearance, cholesterol ratios, glucose level) - Even though multiple variables are measured and a single result is calculated, the device does not incorporate a unique interpretation function, but rather provides standard interpretation of the individual variables that clinicians could do themselves.”*
- *“Common, public demographic risk calculations (e.g., Gail Index, Framingham Risk Score) – These types of calculations are generally freely available to the clinical community, through wide dissemination in peer-reviewed publications, practice guidelines, etc. Clinicians are able to use and interpret this type of calculation in the context of their own clinical knowledge and generally accepted information from the clinical community”*



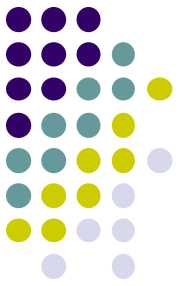
In Vitro Diagnostic Multivariate Index Assays (IVDMIA)



- Classification is based on the intended use and level of controls necessary to assure S&E
- Example: a device intended as an indicator of a patient's risk of cancer recurrence may be a Class II device, while the same device intended to predict which patients should receive chemotherapy might be a Class III device

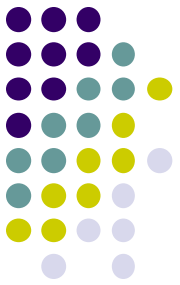


PART 2: IDE Maintenance and Additional Device Studies



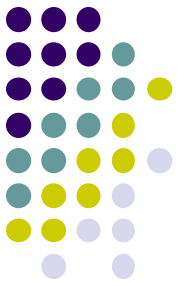
- IDE Maintenance
- *In Vitro* Diagnostic (IVD) Devices
- IVD Multivariate Index Assay (IVDMIA)
- Additional Type of Device Studies
- Case Studies

Additional Types of Device Studies



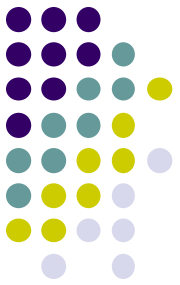
- Early and expanded access
- <http://tinyurl.com/yhkv7o2>
- Emergency Use of Unapproved Medical Device
An IDE might or might not have been approved
Life-threatening situation that needs immediate treatment
There is no generally acceptable alternative for treating the patient
There is no time to use existing procedures to get FDA approval
Must be reported to FDA, IRB within 5 days

Additional Types of Device Studies



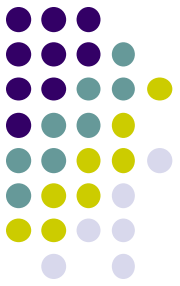
- Single Patient or Compassionate Use
 - Serious condition for which device is the only option
 - Patient do not meet inc/exc criteria
 - Prior approval of FDA and IRB is required
 - Time-frame: during clinical trial

Additional 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

Additional Types of Device Studies



▪ Continued Access

- trial is completed and marketing application is being prepared
- there is a public health need for the device
- preliminary evidence shows that device is likely to be effective and no significant safety concerns have been identified

Difference: Treatment IDE vs Continued Access

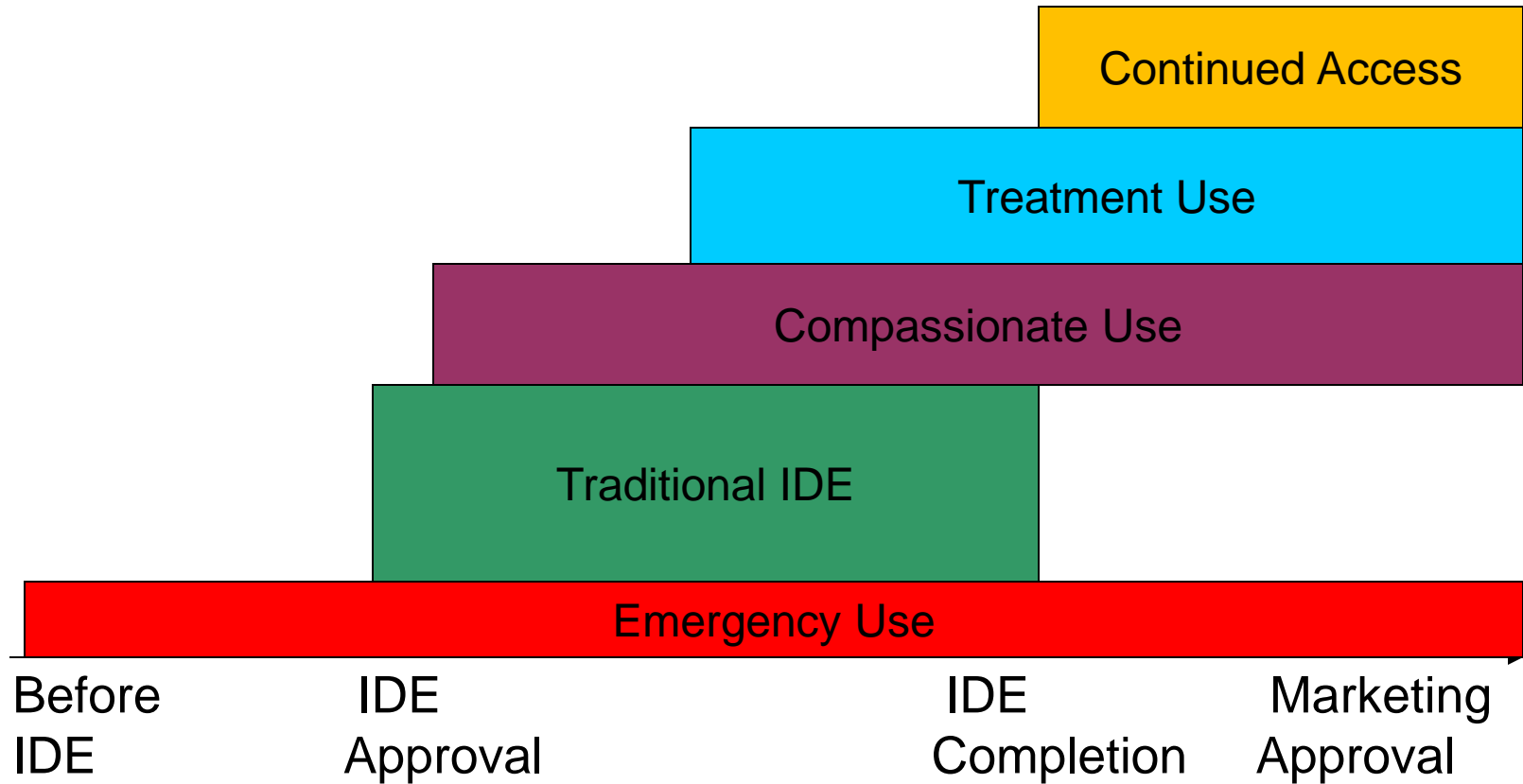
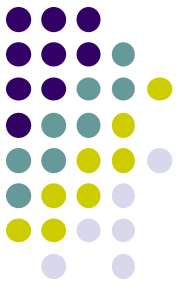
- For Treatment IDE you can apply earlier
- Treatment has more narrow patient population

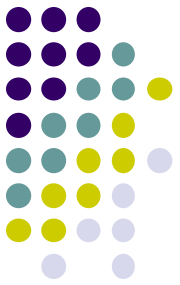
Additional Types of Device Studies



- Humanitarian Device Exemption 21 CFR (814.100)
- An Humanitarian Use Device (HUD) is 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 application is similar to PMA but is exempt from the effectiveness requirements.
- With exception of emergency use, even if used per its approved label, the use of HUD requires IRB approval

Additional Types of Device Studies





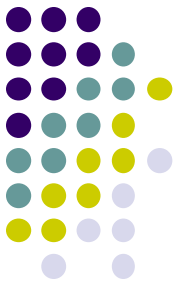
Case Scenario



DTMI

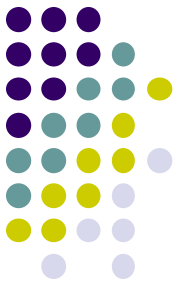
Transforming Medicine

Scenario 1



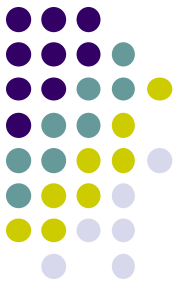
- Investigator is planning on assessing the safety and effectiveness of two different oncology drugs in patients with certain type of lymphoma.
- The patients will be assigned to the therapy based on their genomic profile.
- In order to conduct the profiling step, tumor biopsy will be performed regardless of tumor position.
- If the tumor biopsy is not completed as a part of clinical care, it will be performed for the research purposes only.

Scenario 1



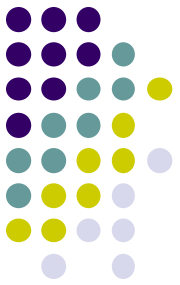
- Q1: Is this a device study?
- Q2: What is an investigational device?
- Q3: Can this study be IDE exempt?

Scenario 2



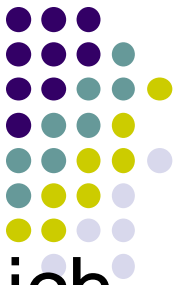
- Investigator is planning on treating depression with **Electroconvulsive therapy (ECT)**.
- Investigator developed a calculation where based on the a few parameters such as: 1) previous drug treatment; 2) score on a mood disorder scale; 3) suicidal attempts; 4) BMI – therapy will be applied either twice a week or once a week.
- The ECT is conducted with the use of ETER.
- Objective of the study is to assess if the assignments based on this calculation is effective.

Scenario 2



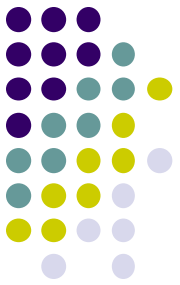
- Q1: Is this a device study?
- Q2: What is an investigational device?
 - ETER?
 - Calculation (Algorithm)
 - Both?

Scenario 3



- The objective of the study is to assess which of the 2 FDA-approved imaging devices provides better images for diagnosis and evaluation of stroke
- The devices used in the study are: 3D Volumetrics scanner and Siemens Antares scanner and appear to be used per their approved label

Useful Websites:

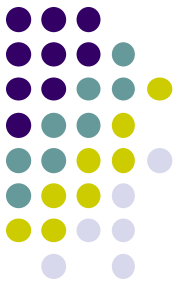


CDRH Learn Course List

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

Device Advice:

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



Thank you!

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or

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