Great Expectations: IND & IDE Determinations

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Great Expectations: Objectives

- Highlight what FDA expects the IRB to expect from sponsor-investigators.
- Describe a step-wise process for determining when a study may require an Investigational New Drug (IND) or Investigational Device Exemption (IDE).
- Provide resources to aid investigators in submitting to and corresponding with the IRB and/or FDA.

(Handout - Slides, FDA Resources & Select Definitions, Glossaries, Applicable Regulations)

August 2013 Final FDA Guidance for IRBs, Investigators, and Sponsors

Guidance to clarify IRBs’ responsibilities in 3 areas.

1. Evaluating the investigator’s qualifications
2. Assessing adequacy of research sites
3. Questioning or determining whether an Investigational New Drug (IND) / Investigational Device Exemption (IDE) is needed.


Gravity and Context

Excerpts from blogs, articles, etc

- “The IRB is expected to assess adequacy of site, staff, equipment, emergency care”
- “FDA expects IRB pay attention to qualifications when investigator is proposing to act as a sponsor-investigator, particularly when outside of the investigator’s area of expertise …”
- “FDA expects IRBs to check an investigator’s inspection history and warning letters”

FDA suggests additional verification of personnel or facilities the IRB has no knowledge of.

FDA recommends IRB reliance agreements define how responsibilities will be divided and carried out.

IND/IDE determinations

“In general, the IRB should ask the investigator if he/she considered whether an IND or IDE is required and the basis for that determination.” August 2013 FDA Guidance

IRB should obtain and evaluate sponsor’s explanation or justification as to why sponsor (sponsor-investigator) believes no IND/IDE needed and if unresolved, delay approval until resolved.
IND/IDE determinations

- Complex framework - diverse products and ‘product-specific’ criteria; still some subjectivity
- Drug (CDER) and Device (CDRH) divisions differ
- Terminology may be confusing.
- Guidance, Forms, Process, … – still presumes that investigator recognizes when conducting FDA regulated clinical investigation in order to make an initial determination if IND or IDE is needed.

What FDA Expects at Inspections ….

- “FDA has also provided instructions to its field investigators on the types of records that should be reviewed during an IRB inspection to determine whether the IRB performed an evaluation of an investigator’s qualifications, assessed the adequacy of a site, and questioned whether an IND or IDE is necessary,” August 2013 FDA Guidance
- FDA Field Guide
  www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoringUCM133768.pdf

Stepwise Process

Drugs & Biologics
21 CFR 312

Investigational New Drug

IRBs should ask…whether the sponsor determined that an IND is or is not required and the basis for the determination”. August 2013 FDA Guidance

1. Is it a drug/biologic?
   - Drug - “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease . . .” and “articles (other than food) intended to affect the structure or function of the body…” [section 201(g)(1) of the FD&C Act]
   - Biologic - virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component …allergenic product, protein applicable to the prevention, treatment, or cure of a disease or condition of human beings. [section 351 of the Public Health Service Act]

2. Is it a Clinical Investigation?
   Yes if study:
   ✓ is an experiment in which a drug is administered or dispensed to one or more human subjects.
   ✓ May involve investigational product or “Investigational Use” of an approved product in the context of a clinical study protocol.

Generally No if:
⊙ Only involves “Clinical Use” –includes only drugs used in the course of medical practice (e.g., antiemetic, rescue inhaler, anesthetic)

If answer is YES 1 & 2 - INCLUDE FDA LANGUAGE IN CONSENT /AUTHORIZATION DOCUMENTS
3. Would the Clinical Investigation meet criteria for Exemption from IND requirements?

  

- 2004 FDA Guidance - IND Exemptions for Marked Drugs /Biologics for Treatment of Cancer
  

Marketed Drug Exemption

If all of the criteria for an exemption in 21 CFR 312.2(b) met.

- Lawfully marketed in US
- No intent to report to FDA to support new indication or labeling change
- For prescription drug, no intent to support change in advertising
- Does not involve route of administration, dose, population or other factor that significantly increases risk or decreases acceptability of risk
- Study is conducted in compliance with FDA IRB review and informed consent regulations
- Investigation is not intended to promote drug product

Guidance provides interpretation exempt criteria – where latitude:

- Route of Administration – described very little latitude; guidance lists concerns with sterility, hypersensitivity, metabolic variations, etc.
- Dose – some latitude in certain therapeutic areas (e.g., oncologists are familiar with implications of high dose, combo regimens)
- Population – healthy vs. debilitating disease; children vs. adults; some latitude but depends on toxicity profile, age, past clinical experience, literature.

Pg 6-7 Sept 2013 IND Exempt Guidance & 2004 Exemptions Cancer Research

FDA Warning Letter: marketed drug studies …do not meet Exempt criteria because they involved a route of administration or dosage level that significantly increased the risks (or decreased the acceptability of the risks) associated with the use of this drug product [21 CFR 312.2(b)(iii)]. Therefore, these studies were subject to 21 CFR Part 312 and should have been conducted under an Investigational New Drug (IND) application.

Informed consent failed to ID experimental procedures, disclose alternatives, state possibility that FDA may inspect records, compensation for injury, and reasonably foreseeable risks.


Other Potential Exemptions

21 CFR 312.2 - Each has specific conditions or criteria that must be met in order to qualify for exemption:

- Select in vitro diagnostic biological products
- Select bioavailability or bioequivalence studies
- Select types of cold isotopes

If check any of these on Form O, follow the link to ensure all conditions or criteria are met.

FAQs:

Do I need an IND if study uses home-made version of a lawfully marketed drug? (methacholine)?

Do I need an IND if study enrolls small number of subjects?

Do I need an IND if study enrolls only health volunteers?

Do I need an IND if no intent to investigate drug’s potential for commercial sale?

Unless study meets exempt criteria, then yes.
4. Need IND

FDA Resources for Investigator-Initiated IND


4. Unresolved? FDA Contacts re IND:

2013 IND Exemption Guidance –
“contact the Chief, Project Manager in the appropriate review division (i.e., therapeutic area being studied)”

CDER – drug info number 301-796-3400
CDER Org Chart, Offices & Divisions, Leadership Bios -
www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/default.htm
CBER – biologics info number 301-827-2000
CBER Office & Divisions, Contact lists
www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/default.htm

Drug definition not limited to compounds intended for therapeutic purpose:

- Drug - “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease …” and “articles (other than food) intended to affect the structure or function of the body” (section 201(g)(1) of the FD&C Act)

Sept 2013 FDA IND Guidance

Dietary Supplement Regulation

Dietary Supplement Health and Education Act (DSHEA) of 1994

- Dietary ingredients in these products can include vitamins, minerals, herbs and other botanicals, amino acids, other dietary substances intended to supplement the diet, and concentrates, metabolites, constituents, extracts, … pill, liquid, powder, bar,…

- No pre-market approval process that requires pre-clinical testing (animal/toxicology) and Phase 1-3 clinical trials.

- Manufacturers only required to notify FDA if supplement contains a “new dietary ingredient” not marketed before 10/1994; ensure claims on product label are truthful; some GMP requirements & submit associated serious AE reports.

- FDA only takes action against adulterated or misbranded supplements after they reach the market.

- FDA issues consumer alerts -
http://www.fda.gov/Food/RecallsOutbreaksEmergencies/SafetyAlertsAdvisories/default.htm

Dietary Supplement Research - need for IND based on intent of study

- Human research on dietary supplement and other Generally Recognized as Safe (GRAS) materials would not require an IND if study is designed to assess affect on structure or function of the body.

(fiber supplement affect on gastric motility)

- However, if intent is to evaluate ability to diagnose, cure, mitigate, treat, or prevent a disease then study is FDA regulated and subject to IND requirements.

(a soluble fiber supplement affect on type II hyperlipidemia)

Dietary Supplement – need for IND based on intent of study

<table>
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<tr>
<th>STRUCTURE/FUNCTION</th>
<th>THERAPEUTIC</th>
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<tr>
<td>No IND</td>
<td>Yes IND</td>
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- Effect on gastric motility Treatment of constipation
- Effect on bone mass Prevention of osteoporosis
- Effect on max O2 uptake Increased exercise capacity heart failure patients
Conventional Food – need for IND

• Therapeutic use? Yes, need an IND

• Affect Structure or Function?
  Depends:
  – No, if affect is based on “food characteristics” – taste, aroma, and nutritive value.
  – Yes, if affect is based on any other characteristic. (e.g., blocks absorption of carbohydrate in the gut)

• *Intent to support a health claim?
  Depends:
  – No, if substance-disease relationship being studied and is already the subject of an FDA authorized health claim
  – Yes, for a new or expanded health claim

FDA Warning Letters – marketers

Product claim in the labeling that cause it to be considered as “misbranded” or “unapproved drug”.

hempseed is one of the most nutritious plant foods available with . . . a near-perfect composition of the essential fatty acids, Omega 3s. These good fats are necessary for optimum health by lowering cholesterol...

not generally recognized as safe and effective for the above referenced conditions and therefore, the product is also a “new drug”.


FDA Warning Letter – human research

"Informed consent states (M-Cosmetics) will use volunteers to test an eyelash growth-enhancing product... " This statement regarding eyelash growth makes clear that this product is intended to affect the structure or function of the body of man or other animals and therefore causes your product to be subject to regulation as a drug."

Cosmetics – need for IND

• Therapeutic use? Yes, need an IND

• Affect Structure or Function? Yes, need an IND

“even if the study is intended to support a cosmetic claim about the ingredient or product’s ability to cleanse, beautify, promote attractiveness, or alter the appearance”

Example: Research on skin repair affects of a product with biological material ingredient, to support a claim of "younger looking skin”.

Problematic for Investigators

Problematic for investigators

Feb 6th FDA REOPENED comment period on Final IND Guidance

The Federal Register Notice provides instructions for submitting comments and link to comments already submitted.

Medical Device Research
21 CFR 812
Investigational Device Exemption

IDE Regulations – 3 types of device Studies

1. Is ‘it’ a Medical Device?

- may include a component, part, accessory, assay, battery, reagent, software, if intended to affect the structure or function of the body, diagnose, cure, mitigate, treat or prevent disease.
- may be therapeutic or diagnostic.
- Section 201(h) of the FD&C Act

FDA Website – Is the product a Medical Device?
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/ucm051512.htm

Mobile Medical Apps (MMA)

Not all apps are MMAs

MMA = meets definition of device and is intended to be used as an accessory to a regulated medical device; or transform a mobile platform into a device.

Mobile Medical Apps (MMA)

Not all MMAs require FDA oversight.

FDA - regulatory oversight to narrow sub-set of apps that transform a mobile platform into a medical device and those where functionality could pose a risk to patient safety if it failed to work, if the screen size distorted radiologic image, etc.
FDA’s MMA Guidance – Sept 2013

<table>
<thead>
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<th>Mobile Apps that are NOT medical devices</th>
<th>May meet definition of medical device but so low risk, FDA intends to “Exercise Enforcement Discretion”</th>
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<tbody>
<tr>
<td>Reference textbooks</td>
<td>Tools to help patient’s track health information, reminders, guide a user through risk factor assessment.</td>
</tr>
<tr>
<td>General patient education</td>
<td>Automate simple tasks for healthcare providers, perform simple calculations (BMI, APGAR), Transfers or displays medical device data (transfer fetal heart rate to smart phone to allow remote monitoring).</td>
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<tr>
<td>MMAs that are focus of FDA oversight</td>
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Determining if Mobile App is a Medical Device that is subject to FDA oversight:

Identify which category your app is most like and provide applicable section of guidance for IRB to reference in considering if the MMA is equivalent to those FDA does or does not wish to regulate.

If unable to find equivalent example in the guidance, Contact the:
Division of Small Manufacturers, International and Consumer Assistance (DSMICA).
Email: dsmina@fda.hhs.gov; phone: 301-796-7100 or 800-638-2041.

Proposed bills call for reduction in FDA oversight of health tech industry

The Software Act of 2013
PROTECT Act of 2014
(Preventing Regulatory Overreach To Enhance Care Technology)

2. Device Clinical Investigation:

✓ Study in one or more subjects that collects safety and/or effectiveness data on an unapproved device or a new intended use of an approved device, **(even if no marketing application is planned)**.

21 CFR 812
Source: CDRH Learn Lynn Henley

2. Clinical or Basic Physiologic Research
**(not a clinical investigation):**

- Uses a device to illicit a physiologic response and **NO** data is collected about the device;
- Uses a device to address a research question and **NO** data is collected about the device; or
- Uses a device to measure a clinical outcome and **NO** data is collected about the device

Basic Physiologic Research or Clinical Investigation?

Consider study objective or purpose:
- We hope to learn about the usability (test efficacy) of ___ software program we are developing…
- Study will use a transcranial direct current stimulation (cause a physiologic response) then (measure) reaction-time.
- The Echo is being used to take images in order to determine which result parameters are the most accurate to quantify X condition (used to answer a question).
Basic Physiologic Research or Clinical Investigation?

<table>
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<th>Study looking at how well the device works in measuring something.</th>
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<tr>
<td>Study using device to measure something but study will collect limited validity data just to demonstrate that the measurements made by device are reasonably accurate.</td>
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<tr>
<td>Study collects only feasibility data on a device.</td>
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<tr>
<td>A low-risk device is used only to address a research question, however the device is homemade.</td>
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Source: Answers to follow up questions 1/30/14 PRIM&R Webinar

3. Would the Clinical Investigation meet criteria for Exemption from IDE requirements?

21 CFR 812.2 IND regulations include several categories of exemptions, however each category has criteria or conditions that must be met to qualify!

Marketed Devices used in accord with Approved Indications / Labeling

Approved device – Approved indication

- Attach materials to illustrate use in study is akin to FDA approved indications:
  - sponsor/manufacturer info
  - approved labeling,
  - contraindications, precautions,
  - FDA or sponsor correspondence
  - Patient information packet

Search Device Clearances & Approvals for Labeling

www.fda.gov/medicaldevices/productsandmedicalprocedures/

In Vitro Diagnostic Device Exemption

In Vitro Diagnostic Device may be exempt IF:
1. Properly labeled - "For Research Use Only. Not for use in diagnostic procedures."
2. Doesn’t require an invasive procedure that presents significant risk.
3. Doesn’t introduce energy into a subject.
4. Results are not used to make clinical decisions (standard of care used for clinical decisions; results confirmed with a medically established diagnostic product or procedure.)

In Vitro Device FAQ


Other Potential Exemptions (rare)

21 CFR 812.2 - Each has specific conditions or criteria that must be met in order to qualify for exemption

- A device undergoing consumer preference testing, testing of a modification, or testing of a combination of 2 or more marketed devices, if testing is not for determining safety or effectiveness and does not put subjects at risk.

- Select Off-the-shelf (OTS) software IF part of an Exempt In Vitro Diagnostic device (4 in-vitro exempt criteria met). Other Software is subject to IDE requirements. See FDA OTS Guidance – www.fda.gov/downloads/medicaldevices/deviceRegulationandGuidance/GuidanceDocuments/UCM073779.pdf

- Custom Device – INDIVIDUAL PATIENT
If device is used in a study and data collected, then it is NOT a custom device.


FDA Warning Letter: marketed device

Tissue repair device, a significant risk device intended use of soft tissue …procedures such as general and orthopedic surgery.” Indicates on clinicaltrials.gov that the endpoint classification for this study is an “efficacy study”. FDA considers disc herniation repair to be a new intended use (outside the scope of 510(k) clearance), because it alters the therapeutic effect (i.e., tissue type, disease entity/target population, and effect on clinical outcomes), risk profile for a spinal implant contains additional risks not present in orthopedics (e.g., neurological), …and SOC for disc herniation does not involve an implanted device.

4. NSR/SR determination- Who?

Sponsor or Sponsor-Investigator

Convened IRB must review justification and make its own NSR/SR determination – document in minutes

If different, IRB must inform sponsor-investigator and delay approval until resolved

FDA Final Arbitrator

NSR Device Category

- Level of risk that doesn’t warrant involvement of FDA.
- Device that based on how it is used in study – Does NOT meet significant risk definition.
- IRB advised to think in terms of device working properly (not worst case scenario).
- No IDE submission, progress reports or final reports to FDA.
- Still involves following the abbreviated IDE responsibilities - covered in mandatory training.

SR Device Studies…

- presents a potential for serious risk to the health, safety, or welfare of a subject....
  - an implant
  - designed to support or sustain human life
  - substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health
- must submit an IDE and obtain approval or conditional approval of IDE from FDA before they may proceed.
- must follow ALL of the IDE responsibilities including all abbreviated plus data monitoring and ongoing FDA reporting.

Jan 2006 FDA SR/NSR Guidance


A. Nonsignificant Risk Devices

Caries Removal Solution
Digital Mammography
Externally Worn Monitors for Insulin Reactions
Magnetic Resonance Imaging (MRI) Devices within FDA specified parameters
General Biliary Catheters

B. Significant Risk Devices

Surgical Lasers
Epidural and Spinal Needles
Cardiac Bypass Devices
Intravascular Stents
Replacement Heart Valves
Intraocular Lenses (IOLs)
Extended Wear Contact Lens

5. Uncertain? FDA Device Contacts

Questions about whether a product is subject to IDE – IDE section of Office of Device Evaluation (ODE) call 301-796-5640 [Marjorie Shulman]
email dsmica@fda.hhs.gov

CDRH Directory, Contact lists, etc.-
www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/default.htm

www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHOffices/ucm127854.htm

5. Contacting FDA – Pre -IDE

FDA PRE Submission Guidance – Feb 18, 2014
“Q-Submission” – Q123456
Primary reason – feedback on study design or statistical analysis

1. detailed device description
2. the protocol for the study
3. a description of how the device will be used
4. a description of the population
5. the sponsor’s name and contact person(s), including titles, address, phone number, fax number, and email address

FDA Regulated & study must fit in 1 of 3 categories

- Exempt from IDE Requirements
- IRB Review per FDA Reg
- FDA in Informed Consent
- IRB Approval
- Subject to IDE Requirements - Full IRB
- Abbreviated IDE Requirements
- SR
- FDA & IRB Approval
- Full IDE Regulatory Requirements

Sponsor-Investigator (SI) Regulatory Responsibilities Summaries

- Devices - IDE & Abbreviated IDE
  Summary of Responsibilities
  Includes labeling, IRB approval, informed consent, monitoring, records, medical device event reporting (adverse events, malfunctions), registering on clinicaltrials.gov, prohibition against promotion, FDA reporting requirements (addendums, annual reports).

- Drugs/ Biologics – IND
  Summary of Responsibilities

Sponsor-Investigator (SI) Regulatory Responsibilities Training

- CITI Sponsor Investigator Training
  Device Development for Sponsor Investigators (GCP) Course for Clinical Trials Involving Investigational Medical Devices

- CITI Sponsor Investigator Training
  Drug Development for Sponsor Investigators – Good Clinical Practice (GCP) GCP Course for Clinical Trials Involving Investigational Drugs

UK IRB SI Mandatory Training Information
www.research.uky.edu/ori/human/HSPtrainingFAQanswers.htm#SICITI

Summary

- FDA has specific expectations regarding IRB review of FDA regulated research.
- When submitting protocols for review:
  - Know if the product you are collecting data on is FDA approved/cleared or not,
  - Reference key guidance documents to determine if subject to IND or IDE requirements,
  - Complete applicable forms (form O or P) to indicate which regulatory category applies, and
  - Include supporting documentation or FDA correspondence.
  - If seeking a determination from FDA, be specific as to what determination you are seeking and provide response to IRB.

Questions

ADDITIONAL RESOURCES

- IRB Chairs & Members with expertise
- UK IRB Forms
- UK & FDA Guidance
- FDA Websites
- FDA CDER & CDRH Learn
- Other areas of FDA/IRB interaction (Emergency/Expanded Access/HUD)
- Other FAQs
UK IRB Forms help document

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<th>FORM P – Devices</th>
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<td>Product details and approval status.</td>
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<td>Section B</td>
<td>1. Exempt from IND requirements</td>
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<td>2. Requires IND submission to FDA</td>
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<tr>
<td></td>
<td>1. Exempt from IDE requirements</td>
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<td></td>
<td>2. Non-Nonsignificant Risk Device - subject to “Abbreviated IDE” under purview of IRB</td>
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<tr>
<td></td>
<td>3. Significant Risk Device – subject to full IDE requirements including IDE submission to FDA</td>
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<tr>
<td>Section C</td>
<td>Product Management, Accountability, Qualifications, Training</td>
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<tr>
<td>Section D</td>
<td>Responsibilities for Sponsor-Investigator – knowledgeable re regulatory obligations when acting as sponsor of IND or IDE</td>
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One time Sponsor-Investigator GCP Training

FDA IND Guidance and Consultation

Pre-IND Consultation and Contact List

Pre-IND Consultation Contacts

Information for Sponsor-Investigators Submitting Investigational New Drug Applications (INDs)

Additional Nutrition Product Guidance

• Complementary and Alternative Medicine Products and their Regulation by the Food and Drug Administration
  www.fda.gov/RegulatoryInformation/Guidances/ucm144667.htm
• Botanical FAQ - www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm069989.htm
• Probiotics - www.usprobiotics.org/
• New Dietary Ingredients in Dietary Supplements
  www.fda.gov/Food/DietarySupplements/ucm109764.htm
• Medical Foods FAQ - under MD supervision (e.g., for inborn error of metabolism – reduced phenylalanine for PKU)
  www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/MedicalFoods/ucm054048.htm

CDRH Learn
CDER Learn

• Regulatory requirements for medical devices - http://fda.yorkcast.com/webcast/Viewer/?peid=040308365ec8405bad39b06de8561bdc1d

• What is an IDE?
  http://fda.yorkcast.com/webcast/Viewer/?peid=855ad7df9054febb5ef004e359ad1e1d

UK & FDA Device Guidance

• UK IRB Review of Medical Device Research
• UK Medical Device SOP
  www.research.uky.edu/ori/human/SOPs & Policies.htm#3
• FDA FAQ about Medical Devices

Early Expanded Access Program Resources

UK Guidance:
• Emergency and Early/Expanded Access Program (EAP) for Drugs and Devices (Summary)
  www.orifacets.org/34-Euse_&_Expanded_Access.pdf
• UK SOPs - www.research.ksu.edu/ori/human/SOPs & Policies.html#3

EAP Training:
• American Society of Clinical Oncology (ASCO)– Drug Expanded Access Training - Guest Access - http://university.asco.org/expanded-access-introduction
• FDA Device EAP - http://www.fda.gov/Training/CDRHLearn/ucm180876.htm
If developing a product – FDA recommends early involvement

FDA Device PRE-Submission program – finalized 2/18/2014

PRE-IND Consult Program
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm#preIND

• FDA draft guidance on IDE for early feasibility device studies including first in human studies
Offers some flexibility
www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm277670.htm

VIDEO PRESENTATION
www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHInnovation/default.htm


Sponsor or Sponsor-Investigator must register studies that meet definition of "Applicable Clinical Trial".

• Does the definition of "Applicable Clinical Trial" under FDAAA 801 ONLY include studies conducted under an FDA IND or IDE?

Answer: No, under FDAAA 801, a clinical investigation of a drug can be an Applicable Drug Clinical Trial even if it does not require an IND, and a clinical investigation of a device can be an Applicable Device Clinical Trial whether or not an IDE is required.

• See Elaboration of Definitions of Responsible Party and Applicable Clinical Trial (PDF) for more information:

Expedited Review FAQ?

• Can a drug or device study be initially reviewed using Expedited IRB review?

Answer: Yes. Minimal Risk Studies that meet Category 1 Expedited Criteria: Clinical studies of drugs & medical devices only when condition (a) or (b) is met.

a. Research on drugs where IND is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)

b. Research on medical devices for which (i) an IDE is not required (e.g., IDE exempt in vitro diagnostic); or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling (e.g., IDE exempt approved device/approved use).

Required Consent Statement (Clinicaltrials.gov)

"A description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time."

Indicate for IRB if the sponsor-investigator has determined study does not meet the “Applicable Clinical Trial” definition.

FAQ: What if during an IRB inspection, FDA disagrees with an NSR determination?

Happened during routine inspection at a private IRB. Sponsor had provided justification and Convened IRB documented deliberation and determination. No foul, ALL EXPECTATIONS MET, however…

FDA required the IRB to suspend study until sponsor obtained a full IDE.

IRB added statement to approval letter – “These determinations are subjective and FDA could, if asked, reach a different decision.”

Humanitarian Use Device (HUD) Resources

UK Guidance:
• UK Summary -Humanitarian Use Devices (HUD)
• ORIForms/54-HUDHOJK.pdf
• UK HUD SOP
• www.research.uky.edu/ori/human/SOPs & Policies.html#3

Training:
• CITI Humanitarian Use Devices
• Optional courses on UK CITI curriculum
www.citiprogram.org
Food and Drug Administration (FDA) Resources

General

• 2009 FDA Guidance on Investigator Responsibilities

• 2013 FDA Investigators, and Sponsors IRB Responsibilities for Reviewing the Qualifications of Investigators, Adequacy of Research Sites, and the Determination of Whether an IND/IDE is Needed

Drug Research

Drug (Food Drug and Cosmetic Act) = “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease...” and “articles (other than food) intended to affect the structure or any function of the body of man or other animals.” Biological products subject to licensure under section 351 of the Public Health Service Act (42 U.S.C. 262) may also be considered drugs within the meaning of the FD&C Act. It is important to note that the drug definition is not limited to compounds intended for therapeutic purpose but also includes compounds intended to affect structure or function of the body without regard to influence on a disease process. [Source 2010 FDA Investigational New Drug Applications (IND) Guidance]

• Drug Approvals and Databases - http://www.fda.gov/Drugs/InformationOnDrugs/default.htm

• 2013 FDA Determining Whether Human Research Studies Can Be Conducted Without an IND

• University of Kentucky (UK) Summary of FDA Exemption from IND Requirements

• 2004 FDA Guidance on IND exemptions for marketed products in cancer treatment

• PRE-IND Consult Program
  http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm#preIND

• FDA information for Sponsor-Investigator’s submitting an IND
Food and Drug Administration (FDA) Resources

- **FDA IND TABLE of links to information for Investigator-Initiated IND Applications**

- **FDA IND website**

- **FDA New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat *Clostridium difficile* Infection Not Responsive to Standard Therapies** - while FDA develops policies, they intend to exercise enforcement discretion providing physician obtains informed consent stating treatment is investigational and including risks.

**Expanded Access Drugs**

- **Expanded Access to Investigational Drugs Treatment Use & Charging for Investigational Drugs**

- **UK Expanded Access SOP**
  [http://www.research.uky.edu/ori/SOPs_Policies/C3-0300-Expanded_Access_Program-for-Drugs.doc](http://www.research.uky.edu/ori/SOPs_Policies/C3-0300-Expanded_Access_Program-for-Drugs.doc)

- **ASCO Expanded Access Course**
  [http://university.asco.org/expanded-access-introduction](http://university.asco.org/expanded-access-introduction)

- **CDER Learn Expanded Access Training**

**Dietary Supplements, Botanicals, Complementary Medicine Research**

- **FDA Determining Whether Human Research Studies Can Be Conducted Without an IND-Section VI.C.**

- **FDA FAQ on Botanical Drug Products**
  [http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm 090989.htm](http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm 090989.htm)
Food and Drug Administration (FDA) Resources

• FDA Complementary and Alternative Medicine Products
  http://www.fda.gov/RegulatoryInformation/Guidances/ucm144657.htm

• New Dietary Ingredients in Dietary Supplements
  www.fda.gov/Food/DietarySupplements/ucm109764.htm

• Medical Foods FAQ - under MD supervision (e.g., for inborn error of metabolism – reduced phenylalanine for PKU)
  www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/MedicalFoods/ucm054048.htm

Emergency Use

• FDA Emergency Use of Investigational Drug or Biologic
  http://www.fda.gov/RegulatoryInformation/Guidances/ucm126491.htm


Device Research

Device (Food, Drug & Cosmetic Act) - A medical device is an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them, intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body .... and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

• 2006 FDA Frequently Asked Questions about Medical Devices

• 2006 Significant Risk and Nonsignificant Risk Medical Device Studies

• UK Summary of FDA Exemption from IDE Requirements

• FDA PRE-IDE Submission Guidance
  http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM3...
Food and Drug Administration (FDA) Resources

- FDA IDE website
  http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046706.htm

- In Vitro Diagnostic (IVD) Device Studies – FAQ

- UK IRB Review of Device Studies

- 2013 FDA Decisions for Investigational Device Exemption (IDE) Clinical Investigations (Approval with conditions)

- 2013 FDA Mobile Medical Applications (Apps that meet the definition of medical device)

- UK Medical Device SOP (includes investigations, compassionate and treatment use)
  http://www.research.uky.edu/ori/SOPs_Policies/C3-0150_Medical_Devices.doc

- 2013 IDE Exemptions for Early Feasibility Studies including certain First in Human (FIH) Studies
  http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm277670.htm

Expanded Access Devices

- FDA Early & Expanded Access Investigational Devices- Compassionate, Treatment, & Continued Access
  http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm051345.htm
Food and Drug Administration (FDA) Resources

Humanitarian Use Device (HUD) Resources

- 2010 FDA HUD Guidance
  http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm110194.htm

- UK Summary Guidance for HUDs
  http://www.research.uky.edu/ori/ORIForms/54-HUDHOJK.pdf

- UK HUD SOP

FDA CDRH Learn Video Presentations

- Regulatory requirements for medical devices – William Sutton
  http://fda.yorkcast.com/webcast/Viewer/?peid=040308365ec8405bad39b06de8561bdc1d

- What is an IDE? -Lynn Henley
  http://fda.yorkcast.com/webcast/Viewer/?peid=8553ad7df9054febb5ef0048e359ad1e1d

- Emergency and Humanitarian Use Training -Fabienne Santel, MD
  http://www.fda.gov/Training/CDRHLearn/ucm180875.htm

Combination Drug and Device Research

- FDA FAQ for Combination Products
  http://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm101496.htm

- FDA Office of Combination Products
  http://www.fda.gov/CombinationProducts/default.htm

IND and IDE Responsibilities for sponsor-investigators

- UK Sponsor-Investigator training on CITI- description and instructions
  http://www.research.uky.edu/ori/ORIForms/82-Sponsor-Investigator-Training-Description.pdf

- UK Summary of FDA Requirements For Investigators Who Are Also Considered Sponsors of New Drug
Food and Drug Administration (FDA) Resources

- UK Summary of FDA Requirements For Investigators Who Are Also Considered Sponsors of New Devices

FDA Inspections

- FDA Bioresearch Monitoring (BIMO) program
  [http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133562.htm](http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133562.htm)

- 2010 FDA Guidance for IRBs, Clinical Investigators, and Sponsors

- FDA Clinical Investigator Disqualification

- Preparing for a FDA Medical Device Clinical Investigator Inspection – Allen Lou

Corrective and Preventive Action Plans (CAPA)

- GxP Perspectives

- Northwest University IRB
  [http://irb.northwestern.edu/policies/compliance/corrective-action-plan](http://irb.northwestern.edu/policies/compliance/corrective-action-plan)

Clinicaltrials.gov

- Guidance regarding which trials must be registered by study sponsor (or sponsor-investigator)
  [http://clinicaltrials.gov/ct2/manage-recs/fdaaa#WhichTrialsMustBeRegistered](http://clinicaltrials.gov/ct2/manage-recs/fdaaa#WhichTrialsMustBeRegistered)

- How to register?

- Information on access to UK ‘s account on Clinicaltrials.gov
  [http://www.ccts.uky.edu/BRIC/ClinicalTrialsgov.aspx](http://www.ccts.uky.edu/BRIC/ClinicalTrialsgov.aspx)
FDA Contact Information

- FDA website outlining procedure for responding to inquiries
  http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm126598.htm

- **Drugs - Center for Drug Evaluation & Research (CDER)**
  - 888-463-6332 or 301-796-3400
  - druginfo@fda.hhs.gov

- **Biologics - Center for Biologics Evaluation & Research (CBER)**
  - 800-835-4709 or 301-827-1800
  - ocod@fda.hhs.gov

- **Device – Center for Devices & Radiological Health (CDRH)**
  - 240-276-4040, 301-796-5640, or 800-638-2041
  - industry.devices@fda.hhs.gov
  - CDRHIDE@fda.hhs.gov

- **Division of Small Manufacturers, International and Consumer Assistance**
  - 800-638-2041 or 301-796-7100
  - dsmica@fda.hhs.gov
SELECT DEFINITIONS

Clinical Investigation: “Involves use of a test article (i.e., drug, device, food substance or biologic), one or more human subjects, meets requirements for prior submission to FDA, or results are intended to be part of an application for research or marketing permit” [21 CFR 56.102]

Human Subjects (FDA (Drug, Food, Biologic): “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.” [21 CFR 56.102(e)]

Human Subjects (FDA Medical Device): “A human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control. A subject may be in normal health or may have a medical condition or disease.” [21 CFR 812.3(p)] (Medical Devices) NOTE: This definition includes use of tissue specimens even if they are unidentified.

Drug - articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease . . . and articles (except food) intended to affect the structure or function of the body...
[section 201(g)(1) of the FD&C Act]

Biologic - virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component ...allergenic product, protein applicable to the prevention, treatment, or cure of a disease or condition of human beings. [section 351 of the Public Health Service Act]

Medical Device - intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, ... or intended to affect the structure or any function of the body.

Dietary Supplements (including dietary ingredients)- may include vitamins, minerals, herbs and other botanicals, amino acids, other dietary substances intended to supplement the diet, and concentrates, metabolites, constituents, extracts, or combinations of the preceding types of ingredients. Dietary supplements can also be extracts or concentrates, and may be found in many forms such as tablets, capsules, softgels, gelcaps, liquids, or powders. They can also be in other forms, such as a bar, but if they are, information on their label must not represent the product as a conventional food.

Sponsor-investigator is an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the investigational device is administered, dispensed, or used. The term does not, for example, include a corporation or agency. The obligations of a sponsor-investigator include those of an investigator and those of a sponsor.

Investigational New Drug (IND) application is the vehicle through which a sponsor advances to the next stage of drug development known as clinical trials (human trials). Usually is the result of a successful preclinical development program. Technically, it is a request for an exemption from the Federal statute that prohibits an unapproved drug from being shipped in interstate commerce to reach destination study sites. However, the main purpose is to detail the data to document that it is indeed reasonable to proceed with certain human trials with the drug.
**Investigational device exemption (IDE)** refers to the regulations under 21 CFR 812. An approved IDE means that the IRB (and FDA for significant risk devices) has approved the sponsor’s study application and all the requirements under 21 CFR 812 are met. A IDE allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data. An approved IDE permits a device to be shipped lawfully for the purpose of conducting investigations of the device.

**Additional FDA Glossaries:**


**FDA IDE Definitions and Acronyms** - http://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/investigationaldeviceexemptionide/ucm046698.htm

**Applicable FDA Regulations:**

The primary regulations that govern the conduct of clinical studies are included in the Code of Federal Regulations, Title 21 (21 CFR):

- 21 CFR 312, *Investigational New Drug Application*, covers the procedures for the conduct of clinical studies with drugs including application, responsibilities of sponsors and investigators, and individual emergency and expanded access use.

- 21 CFR 812, *Investigational Device Exemptions*, covers the procedures for the conduct of clinical studies with medical devices including application, responsibilities of sponsors and investigators, labeling, records, and reports.

- 21 CFR 50, *Protection of Human Subjects*, provides the requirements and general elements of informed consent;

- 21 CFR 56, *Institutional Review Boards*, covers the procedures and responsibilities for institutional review boards (IRBs) that approve clinical investigations protocols;

- 21 CFR 54, *Financial Disclosure by Clinical Investigators*, covers the disclosure of financial compensation to clinical investigators which is part of FDA’s assessment of the reliability of the clinical data.

- 21 CFR 820 Subpart C, *Design Controls of the Quality System Regulation*, provides the requirement for procedures to control the design of the device in order to ensure that the specified design requirements are met.