The FDA IND and IDE Regulations, including IVDs

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Agenda

- MIAP Services Overview
- Applicable Regulations and Definitions
- IND Regulations
- IDE Regulations
- Regulation of IVDs and the Draft Guidance Document
MIAP SERVICES OVERVIEW

- Agent/Device development/regulatory strategy consultation
- IND/IDE consultation including determination of need for IND or IDE
- Pre-IND/IDE FDA meeting requests and support
- Protocol/Informed Consent review
- IND/IDE application preparation and submission to FDA
- Clinical hold/conditional approval response preparation/submission
- Communication with the FDA, IRB and other regulatory bodies
- IND/IDE “maintenance” support
  - Safety report submissions
  - Protocol amendments
  - Annual reports
  - Investigator Amendments
  - Informational Amendments

Applicable Regulations

The Federal Food, Drug, and Cosmetic Act (FD&C Act) gives the FDA authority to regulate drugs and devices

Investigational Drugs/Biologics

- Code of Federal Regulations (CFR)
  - 21 CFR Part 312: Investigational New Drugs

Investigational Devices

- Code of Federal Regulations (CFR)
  - 21 CFR Part 812: Investigational Device Exemptions
For BOTH IND and IDE

- **Sponsor** is an individual, company, academic institution, or other organization that takes responsibility for and initiates a clinical investigation. The sponsor is not the “funding organization” by FDA definitions. The Sponsor holds the IND or IDE.

- **Investigator** is an individual under whose immediate direction a drug is administered or dispensed.

**Sponsor-Investigator** is an individual who both initiates and conducts an investigation.

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**Drugs- 21 CFR 312 IND Application**

**IND- Investigational New Drug Application**

Current Federal law requires that a drug be the subject of an approved marketing application (be approved by the FDA-have an approved NDA or BLA) before it is transported or distributed across state lines. IND allows for exemption from these requirements.
Other than allowing a new drug to legally cross state lines, what is the purpose of an IND?

- To ensure subjects will not face undue risk of harm in a clinical investigation that involves the use of a drug.
- To authorize a drug study in humans, the FDA requires sufficient information to **assess the safety** of the intended research study.


What is the FDA definition of a drug?

A drug is defined as:

- A substance recognized by an official pharmacopoeia or formulary.
- A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.
- A substance intended to affect the structure or any function of the body.
- A substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device.
- Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process.)
What can be considered an investigational drug?

- Live organisms (i.e. fecal matter, probiotics)
- Cosmetics
- Botanicals
- Synthetic Compounds
- Endogenous Compounds
- Food
  - Dietary supplements
  - Conventional food
- Drugs on the market that have not been approved by FDA

Any of the above can be considered a drug, if it meets the FDA definition.

FDA Issues Warning Letter to General Mills Objecting to Cheerios® Claims

18 May 2009 | Publication
Authors: Michael D. Flanagan, Richard J. McKenna, David L. Rosen

Legal News Alert: Food

Background

The U.S. Food and Drug Administration (FDA) recently issued a Warning Letter to General Mills, Inc. objecting to claims the company makes on its Cheerios® Toasted Whole Grain Oat Cereal. The letter objects to General Mills’ use of claims about the ability of Cheerios to lower cholesterol levels, which the FDA views as impermissible drug claims. As discussed below, the Warning Letter is noteworthy for a variety of reasons, including the extent that it may have on claims made by both the food and dietary supplement industries. In addition, the letter reaffirms the FDA’s position that statements made on product and company Web sites, an area typically regulated by the Federal Trade Commission (FTC) as advertising, can be regulated by the FDA as labeling if the product’s label includes the Web address to the site where the claims are made.
When is an IND Needed? (21 CFR 312)

**ALL studies that use a drug not approved for marketing by the FDA will always require an IND**

or

Investigator intends to conduct a study with an approved drug, but, it is “off label”...

- in a new indication/population/disease state
- in a new dosage form OR
- in a dosage range that is not covered in the current package insert

And the off label use has the potential to **significantly increase the risk**

Manufacturer supplying commercial or research drug?

How do I decide if a study using approved drugs off label is exempt from needing an IND?

**Significantly Increased risk? Can be complicated**

- Route of Administration
  - Drug approved for oral administration is going to be given intravenously
- Dose
  - Increases in dose, frequency, or duration of administration
  - Decrease in dose
  - Combination therapy
- Patient Population
  - Adult to children
  - Moving from very ill population to a less ill population—such as healthy subjects
Off Label? How do I know? “We do this all the time”...

Find the most recently approved drug label

- Do an online search-NIH Daily Med

Consult FDA Guidance Document

Guidance for Industry
Investigational New Drug Applications (INDs)—
Determining Whether Human Research Studies Can Be Conducted Without an IND

October 2010

Or….Ask MIAP- we might ask the FDA

► MIAP will review the protocol along with the approved drug label
► FDA IND Exemption Request Submission
► Usually hear back within 30 days- concurrent with IRB review
IND Content Requirements per 21 CFR 312.23- MIAP will assist

- Cover Sheet
- Table of Contents
- Introductory statement and General Investigational Plan
- Investigator Brochure (IB)
- Study Protocol and Informed Consent
- Chemistry, Manufacture, and Control Information (via LOA)
- Pharmacology and Toxicology Information (via LOA)
- Previous Human Experience (via LOA)
- Additional Information (ex-informed consent document, References)

Timing of Submission

30 DAYS

- Concurrent with IRB review
- Upload PDF of the submission into eResearch-Section 15
- Usually hear back from the FDA before the study is reviewed by the full IRB Board
During the review period, FDA may request additional information, or protocol changes, on a very short timeline.

After 30 days, the IND can be considered safe to proceed, unless the FDA sends notification otherwise. However, MIAP will always contact the project manager for a Safe to Proceed Letter or email- the IRB will ask for this.
But hold on….IND obligations are just getting started.....You are now a Sponsor Investigator and you must follow the regulatory obligations required.
IND Maintenance - MIAP will assist

IND Amendment
/Documents submitted to an active IND/

- The 4 major types are...
  - Protocol Amendments *(21 CFR Part 312.30)*
  - Information Amendments *(21 CFR Part 312.31)*
  - IND Safety Reports *(21 CFR Part 312.32)*
  - IND Annual Reports *(21 CFR Part 312.33)*

IND Responsibilities

**FDA Submissions - Responsibilities To FDA for an IND (312.32-IND safety reports)**

<table>
<thead>
<tr>
<th>Submission</th>
<th>Timing</th>
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<tbody>
<tr>
<td>Amendment - New protocol</td>
<td>After IRB approval</td>
</tr>
<tr>
<td>Amendment - Changed protocol</td>
<td>At time of change</td>
</tr>
<tr>
<td>Amendment - New investigator</td>
<td>Within 30 days of being added</td>
</tr>
<tr>
<td>Amendment - Information</td>
<td>At time of occurrence</td>
</tr>
<tr>
<td><strong>IND safety report</strong> (Serious and unexpected</td>
<td>Within 15 calendar days of receiving</td>
</tr>
<tr>
<td>suspected adverse reaction, findings from</td>
<td>notification)</td>
</tr>
<tr>
<td>other studies, findings from animal or in vitro</td>
<td></td>
</tr>
<tr>
<td>testing, increased rate of occurrence of serious</td>
<td></td>
</tr>
<tr>
<td>suspected adverse reactions)</td>
<td></td>
</tr>
<tr>
<td><strong>IND safety report</strong> (Unexpected fatal or life-</td>
<td>Within 7 calendar days of receiving</td>
</tr>
<tr>
<td>threatening suspected adverse reaction)</td>
<td>notification)</td>
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<tr>
<td>Annual report</td>
<td>Within 60 days of anniversary of IND</td>
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<tr>
<td>Withdrawal of IND</td>
<td>At time of withdrawal</td>
</tr>
<tr>
<td>Discontinuation of investigation</td>
<td>Within 5 working days of discontinuance</td>
</tr>
<tr>
<td>Financial disclosure report</td>
<td>At time of change</td>
</tr>
</tbody>
</table>
How to Regulate Medical Devices?

FDA Definition of a Medical Device

An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar 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 conditions, or in the cure, mitigation, treatment, or prevention of disease or
- Intended to affect the structure or any function of the body

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 intended purposes.
What is a “Medical Device”?

![Images showing examples of medical devices and non-medical devices]

Apple Watch 4 Is Now An FDA Class 2 Medical Device: Detects Falls, Irregular Heart Rhythm

As a contributor to a platform, I noted that Apple Watch Series 4 that was unveiled on Wednesday is turning into a serious medical device with fall detection and 3 new heart-monitoring capabilities: low heart rate alert, heart rhythm detection, and a personal electrocardiogram (ECG) monitor.
Intended Use

**Intended use**: General purpose of the device or its function, and encompasses the indications for use.

The device intended use(s) is very important.

It will affect how it will be regulated and whether it will be regulated as a medical device.

FDA Definition for Research:

- **Investigational Device**: An investigational device is a medical device that is the subject of a clinical study designed to evaluate the effectiveness and/or safety of the device.

- This can be a device that has not been reviewed or approved by the FDA, or a device that has been approved or cleared and is being used “on label” or “off label”

Note- A legally marketed device used in accordance with its labeling (on label) is exempt from needing an IDE
Medical Devices are Divided into Class and Risk

For Marketing

Class I
Class II
Class III

For Research

Non-Significant Risk- NSR

Significant Risk-SR

Significant Risk (SR) vs. Non-Significant Risk (NSR) Device

- **Significant Risk Devices-Require an IDE from the FDA**
  - Intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject
  - Is for use in supporting or sustaining human life
  - Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease
  - Otherwise presents a potential for serious risk to a subject

- **Non-Significant Risk Devices-Abbreviated IDE**
  No FDA Submission Required
  - Does not meet the definition of a significant risk device
What is the purpose of an IDE?

- An investigational device exemption (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 without complying with other requirements of the Food, Drug, and Cosmetic Act (FD&C Act) that would apply to devices in commercial distribution.

Who decides if a device is SR or NSR?

**Sponsor (or Sponsor/Investigator):**
- Makes the initial risk determination based on the device, the intended use, and other aspects of the clinical protocol
- Presents this info to the IRB
  - Sponsor can decide to ask the FDA

**IRB:**
- Will review the device information (including IFU, description of the device)
- Clinical Protocol

**FDA:**
- If the IRB and the sponsor do NOT agree, the FDA will be asked to make the final determination.
- The FDA’s decision final
Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors

Significant Risk and Nonsignificant Risk Medical Device Studies

January 2006


IDE DECISION WORKSHEET
For Investigator-Initiated Clinical Investigations

Is Your Study an IDE Subsequent to the FDA as well as to the IRB(ED)?

Note: The following worksheet is intended to help determine whether an IDE is required for FDA/IRB/ED approval prior to initiating your Investigator-Initiated Medical Device Clinical Study.

Investigational Device Name & Manufacturer

<table>
<thead>
<tr>
<th>IDE REQUIREMENTS DECISION CRITERIA</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Does the study involve a Medical Device that is being used in accordance with its labeling that has been approved/cleared by the FDA if NO, proceed to question #2. If YES, then an FDA-approved IDE is not required.</td>
<td></td>
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<tr>
<td>2. Medical Device a Diagnostic Device?</td>
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<tr>
<td>3. If answer to question #2 is NO, skip to question #4. If YES and the study will involve a Diagnostic Device, it may be exempt from IDE regulations. According to 21 CFR 812.2(b)(3), a Diagnostic Device may be considered exempt from IDE regulations if: (a) The study does not involve an invasive sampling procedure that presents a significant risk; (b) The testing does not require an invasive sampling procedure that presents a significant risk; (c) The testing is not used as a diagnostic procedure without confirmation of the diagnosis by another, readily established diagnostic procedure; or (d) The study is not intended to provide data for or support a submission to the FDA.</td>
<td></td>
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<tr>
<td>4. Does the study involve an Investigational Device? If YES, proceed to #5. If NO, stop here.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Does the Investigational Device have a Significant Risk? (Yes to 1 or 2) 21 CFR 812.3(a) and 812.30(a)(1)</td>
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http://www.michr.umich.edu/services/regulatorysupport/miap
What are the Requirements for NSR Device Studies?

- Abbreviated IDE requirements per 21CFR812.2(b)
  - Labeling
  - IRB approval
  - Informed Consent
  - Monitoring
  - Record Keeping
  - Reports
  - Prohibition against promotion
- NSR studies are considered to have an approved IDE therefore no IDE is submitted to the FDA
- Sponsors and IRBs do not have to advise FDA of NSR device studies
- IRBs must make a SR or NSR determination for every NSR study (21CFR812.66)

Requirements for an FDA IDE Application (for SR devices)-MIAP will assist

- Name and address of the sponsor
- Complete report of prior investigations of the device
- Investigational Plan, including monitoring procedures
- Description of the methods, facilities, and controls used for the manufacture, processing, packing, storage of the device
- Investigational agreement
- Investigator names, institutions, and CVs
- IRB information
- Amount being charged for the device and explanation why the sale does not constitute commercialization
- Labels
- Informed Consent
- Additional information (draft CRFs)
IDE Application Process

- FDA assigns a special IDE identifier number GXXXXXX
- FDA has 30 calendar days for review - Iterative process - same as for INDs, but typically there is more back and forth
- 44% of submissions are disapproved - reasons for disapproval:
  - Safety
  - Study Design

FDA typically receives 200-250 IDE submissions / year (as opposed to 1600 INDs)

IDE Maintenance

IDE Supplements and Reports (Documents submitted to an active IDE)

Supplements:
- New Protocol
- Change in a Protocol
- New Investigator
- Information

Reports will include:
- Safety report (UADE)
- 6 Month Investigator List
- Annual Progress Report
- Final Report
### IDE Responsibilities

FDA Submissions - Responsibilities To FDA for an *IDE* (812.150)

<table>
<thead>
<tr>
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<tr>
<td>Supplement- New protocol</td>
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</tr>
<tr>
<td>Supplement - New investigator</td>
<td>At time of change</td>
</tr>
<tr>
<td>Supplement - Information</td>
<td>At time of occurrence</td>
</tr>
<tr>
<td>Unanticipated Adverse Device Effects</td>
<td>Within 10 working days of receiving notification</td>
</tr>
<tr>
<td>Recalls and Device Disposition</td>
<td>Within 30 days</td>
</tr>
<tr>
<td>Progress/Annual report</td>
<td>At regular intervals (at least yearly)</td>
</tr>
<tr>
<td>Withdrawal of IRB or FDA approval</td>
<td>Within 5 working days of receipt of notice</td>
</tr>
<tr>
<td>Completion or Termination of investigation – Final Report</td>
<td>Within 30 days</td>
</tr>
</tbody>
</table>

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046717.htm

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### Also Can be Medical Devices

- Diagnostic products including laboratory tests
- Biomarker and genetic sequencing tests
- Software
- Mobile Medical Apps
- Decision Support Tools
- Artificial Intelligence (AI), Machine Learning, and Algorithms
Evaluating the Risk

Most devices—Physical risks to the patient (implant or life sustaining).

What about Software, lab tests (genetic sequencing and biomarker tests), mobile apps, algorithms?

Risk now becomes **what happens if the result is incorrect**
False positives?
False negatives?

Significant Risk (SR) vs. Non-Significant Risk (NSR) Device

**Significant Risk Devices—Require an IDE from the FDA**
- Intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject or
- Is for use in supporting or sustaining human life or
- Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease or
- Otherwise presents a potential for serious risk to a subject

**Non-Significant Risk Devices—No FDA Submission Required**
- Does not meet the definition of a significant risk device
IVD Regulations

In vitro diagnostic products are those reagents, instruments, and systems intended for use in diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae.

**Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. [21 CFR 809.3]**

Regulatory Authority

- IVDs are **medical devices** as defined in section 210(h) of the Federal Food, Drug, and Cosmetic Act, and may also be biological products subject to section 351 of the Public Health Service Act. Like other medical devices, IVDs are subject to premarket and postmarket controls.

- IVDs are also subject to the Clinical Laboratory Improvement Amendments (CLIA '88) of 1988.
IVD IDE Exemption Criteria:

Diagnostic Device Studies, including IVDs can be Exempt from the IDE Regulations - 21 CFR 812.2 (c):

- Is noninvasive
- Does not require an invasive sampling procedure that presents significant risk,
- Does not by design or intention introduce energy into a subject, and
- Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.
- Must comply with labeling requirements of 21CFR809.10(c)

Does NOT meet the IVD exemption criteria and will need a risk determination

- Involves research only sampling procedure other than blood, urine, saliva, or requires obtaining extra biopsy tissue
- Returning results to patients or clinicians without verifying first with an FDA approved or cleared test
- Using results to guide care on the study
IVDs in Therapeutic Drug Trials
FDA Draft Guidance Document

• Issued December 2017

• Clearly still indicates this is “draft” - not for implementation

• However, this reflects the FDA’s current thinking

From the Guidance: Introduction....

► Personalized medicine relies on the use of in vitro diagnostics (IVD) devices to measure biomarkers with the goal of directing treatment.

► The information generated by the use of IVDs in drug trials may affect important aspects of treatment for the enrolled subjects and, by doing so, directly influence the types of therapeutic products or therapeutic management strategies the subjects may be exposed to during the study. Therefore, use of an investigational IVD in a therapeutic drug trial may pose significant risk to subjects.
IND and an IDE could be needed

It is important for sponsors to understand that even if a therapeutic product trial is permitted under the IND regulation (granted an approved IND), or is exempt from the requirements of the IND regulation, **the sponsor must still have an IDE that is approved or approved with conditions by the FDA if the trial includes a SR investigational IVD.**

What is the definition of “Investigational” IVD?

- **A novel IVD** (has not been cleared or approved for marketing by the FDA. What about “laboratory developed test performed in a CLIA certified lab”?)
- **An IVD that is legally marketed in the US for a different intended use**
- **A legally marketed IVD that has been significantly modified** in respect to its technological characteristics
Intended Use in the Trial

- The IVD Intended Use in the trial is key
- Needed to determine if the IVD is SR, NSR, or exempt
- How will test results drive treatment assignment or otherwise influence the clinical management of study subjects?
- The risk is based on the possibility of erroneous results

When can an IVD in these trials be considered SR, and need an IDE based on the Intended Use?

If results of the IVD determines:
- Study Enrollment (inclusion/exclusion criteria)- even if “known positive- testing not performed as part of the trial)
- Predicting Serious Adverse Reactions
- Dosing
- Monitoring
- Assigning subject to study arms
There also could be risks of the sampling procedure

- Invasive sampling (e.g. certain biopsies or sampling procedures) may ALSO introduce significant risk, even if the selection of therapy is not guided by results from the investigational IVD
- The guidance does not give examples

FDA Feedback

- Depends upon the site of the tumor
- The procedure used
- The patient population
- Including (but not limited to) biopsies of the brain, lung/mediastinum, pancreas, or endoscopic procedures extending beyond the esophagus, stomach or bowel.
Device Risk Determination Process remains the same:

- PI makes initial assessment of SR versus NSR
  - If SR must submit IDE to the FDA
  - If NSR present this information to the IRB
- IRB makes SR/NSR determination
- If IRB determines NSR - abbreviated IDE
- If IRB determines SR - PI submits IDE application to the FDA
- PI can ask the FDA CDRH for a risk determination prior to IRB submission – MIAP will assist

MIAP has created a draft Checklist for PIs for IRB submission based on the guidance document for investigators regarding NSR/SR determination for the IVD.
**Informed Consent**

Guidance states:
- ICD should clearly explain the investigational nature of the IVD
- ICD should address risks associated with the consequences of an incorrect test result from the investigational IVD as well as risks associated with the investigational drug
- Also must include risks from the specimen collection procedures

**IND or IDE: Sponsor-Investigator**

- Has both the responsibility of the Sponsor AND the Investigator under the FDA regulations
FDA Policy for Device Software Functions and Mobile Medical Applications: Guidance and FDA Enforcement Discretion

IRBMED Seminar Series
November 5, 2019

Judy Birk, JD
University of Michigan
New Guidance

- Issued 2/9/15; updated September 27, 2019

- Acknowledges the rapid pace of innovation in software applications and mobile apps and the potential health benefits they provide

- Clarifies the subset of software (rather than platform) over which the FDA intends to apply its authority

Scope of FDA Enforcement

- Software
- Functioning as medical devices
- Where there is a risk to patient safety if the software doesn’t function as intended
Enforcement Discretion

- Some software functions may meet the definition of a medical device, but because they pose a lower risk to the public, FDA intends to exercise enforcement discretion over these devices (it will not enforce requirements under the FD&C Act)

- Note: these software/devices remain FDA regulated

Software as a Medical Device

- Deployed to
  - Mobile platforms
    - If meets definition of a device = mobile medical app
  - General-purpose computing platforms
  - Function or control of a hardware device

- Intended for use in the diagnosis or the cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man

- The level of regulatory control necessary to assure safety and effectiveness varies based upon the risk the device presents to public health
FDA Regulatory Oversight: Connecting, Controlling, Analyzing

- Software connected to a medical device for the purpose of controlling the device or analyzing medical device data
  - Mobile platform that controls inflation and deflation of a blood pressure cuff
  - Mobile apps that control delivery of insulin via a pump by transmitting control signals to the pump from a mobile platform
  - FDA considers these accessories to the connected device and they are required to comply with the controls applicable to that connected device

FDA Regulatory Oversight: Transforming

- Software that transforms a mobile platform into a regulated medical device via attachments, display screens, or sensors
  - Attachment of a glucose strip reader to a mobile platform to function as a glucose meter
  - Attachment of ECG electrodes to a mobile platform to measure, store, and display ECG signals
  - Use of the built-in accelerometer on a mobile platform to collect motion information of monitoring sleep apnea
FDA Regulatory Oversight:
Performing Patient-Specific Analysis, Diagnosis, or Treatment Recommendations

- Software that perform sophisticated analysis or interpret data (electronically collected or manually entered) from another medical device
  - Software functions that use patient-specific parameters and calculate dosage or create a dosage plan for radiation therapy
  - Computer Aided Detection (CAD) image processing software

- FDA believes these software functions present the same level of risk to patients regardless of the platform on which they run

FDA Enforcement Discretion

- Help patients (software users) self-manage their disease or conditions without providing specific treatment or treatment suggestions

- Automate simple tasks for health care providers

- These generally pose a low risk to patients
FDA Enforcement Discretion: Provide/Facilitate Supplemental Clinical Care

- Coach patients with conditions such as cardiovascular disease, hypertension, diabetes or obesity
- Promote strategies for healthy weight, nutrition, exercising, staying fit, managing salt intake, predetermined medication dosing schedules

FDA Enforcement Discretion: Provide Access to Information

- Use of a patient’s diagnosis to provide a clinician with best practice treatment guidelines for common illnesses or conditions such as influenza
- Drug-drug interaction or drug allergy look-up tools
FDA Enforcement Discretion: Image Capture for Communication

- Use of a smart phone’s built-in camera or a connected camera to transmit a picture of a wound or skin lesion to a clinician to supplement a verbal description

FDA Enforcement Discretion: Simple Calculations

- Medical calculators for
  - BMI
  - APGAR Scores
  - NIH Stroke Scale
  - Glasgow Coma Scale Score
Manufactures of software should consult with FDA Guidance and FDA if unclear.
Agenda

- IRBMED Review Process: General Overview

- eResearch Application: General Overview

- eResearch application: Drugs, Devices, Mobile applications, etc.
  - When/What/How?

IRBMED Review Process

Once the IRB application is submitted...

- Review by Ancillary Committees
  - Research Pharmacy (formerly IDS) for drug studies,
  - Clinical Engineering Unit (formerly BEU) for certain device studies,
  - Billing Calendar (CRAO), Conflict of Interest (COI) Committee, and any other applicable committees

- Review by IRBMED Regulatory Staff
  - Completion, consistency, regulatory parameters, etc.

- IRBMED Convened Board or Expedited-Review
  - Regulatory Determinations (IND Exemption, Device risk determinations, etc.)
IRBMED Guidance

- Available on the IRBMED Website

- Section 15 Drugs & 16 Medical Devices

- Driven by the “Object of the study” requirement
  - Examples

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eResearch Application: general overview

Relevant application types in eResearch (Section 01-1.1)

- Standard (Human Subjects Research Involving interaction / intervention)
- Secondary Research Use of information or samples
- Multi-site Research...

- Expanded Access Drug or Biologic or Device
  - Emergency Use or
  - Non-Emergency/Compassionate Use

- Humanitarian Use Device (HUD) under a HDE

MIAP is available to assist PIs
Section 15: Drugs, Biologics, etc.

- When to complete or what to list?
  - Follow most recent IRBMED Guidance
  - Intended for Drugs, Biologics, and/or other agents
  - The “objective” of the study requirement
    - A study that is under IND
    - A study that is evaluating/administering a drug for an investigational purpose

- How to complete or What information is needed?
  - Next Slides
Section 15. Drugs, Biologics, etc.

- Trigger questions
  - Answering “Yes” to question 7-1.7 will trigger “Section 15 Drugs”
  - Section 07-1 (Special Considerations) is triggered when question 05.3 is answered “Yes” implying there will be subject interaction/recruitment/enrollment.

Section 15. Drugs, Biologics, etc.

- Section 15 is divided into three sub-sections.
Section 15. Drugs, Biologics, etc.

- Section 15: List the study drug per its current FDA approval status and the intended use in the study

- If the research is to evaluate the impact of pomegranate juice on a health related claim then, pomegranate juice should be listed as a drug in the IRB application, under “Not FDA approved”

- Drug A is approved by FDA for condition X. If a research proposal is evaluating drug A for condition Y then, drug A should be listed under “FDA-approved Agent, Used Off-Label”

- Drug A is approved by FDA for condition X to be used in Adults. If a research proposal is evaluating drug A in children for the same indication, drug A should be listed under “FDA-approved Agent, Used Off-Label” as the targeted subject population is not approved by the FDA.

Section 15. Drugs, Biologics, etc.

Agents Not Approved by the FDA—or—FDA-approved Agents Used “off-label”

- General Information
  - Name of the product
  - Source of the product, any compounding requirements
  - How it is being used/evaluated (as a drug or other product) in the study
  - Information on the proposed use (mechanism of action, route of administration, frequency, etc.)

- IND applicability assessment
  - IND vs IND Exemption
  - FDA IND letter or MIAP IND Worksheet
  - Full IND application (for UM Sponsor-Investigator studies)

- Supporting documents
  - Investigator’s Brochure
  - FDA approved label or package insert
Section 15. Drugs, Biologics, etc.

FDA-approved Agents Used “on-label”

- General Information
  - Name of the product
  - Source of the product, any compounding requirements
  - How it is being used/evaluated (as a drug or other product) in the study
  - Information on the proposed use (mechanism of action, route of administration, frequency, etc.)

- Supporting documents
  - Investigator’s Brochure
  - FDA approved label or package insert

Section 16: Medical Devices
Section 16. Medical Devices

- When to complete or what to list?
  - Follow most recent IRB MED Guidance
  - Intended for “Medical” Devices
  - The “objective” of the study requirement
    - A medical device that is being evaluated as part of the study

- How to complete or What info is needed?
  - Next Slides

Section 16. Medical Devices

Trigger questions

- Answering “Yes” to question 7-2.1 will trigger “Section 16 Medical Devices”
- Section 07-2 (Special Considerations) is triggered when question 05.3 is answered “Yes” indicating that there will be subject interaction/recruitment/enrollment.
Section 16. Medical Devices

For a Secondary Research application type (no interaction with human subjects)

The following question will appear in 01-1.2 Scope of Secondary Use Research. Answering “Yes” to this question will trigger “Section 16 Medical Devices”.

Section 16. Medical Devices

List the medical device per its current FDA approval status and the intended use in the study.
Section 16. Medical Devices

Section 16.2.1 Devices Not Approved/Cleared by the FDA or
Section 16.2.12 Devices FDA Approved/Cleared, Using Off-Label

General information (name, source, manufacturer, intended use, etc.)

IVD question (Is this an in vitro diagnostic device that meets specific criteria?)

- Yes: End of Section 16
- No: Provide Sponsor’s assessment of why NSR or upload MIAP IDE worksheet or upload FDA’s confirmation that the device is NSR

Must select either SR or NSR

- Yes: SR
- No: NSR

FDA’s IDE approval is required

Is the device being tested for safety and/or efficacy?

- Yes
- No

Section 16. Medical Devices

Section 16.2.28 Devices FDA Approved, Using On-Label

- General questions regarding the medical device
  - Name, Source (Manufacturer and Supplier), Intended Use, etc.

- 510K number or PMA number
  - Access FDA Medical Device database, available on FDA website
  - For Class I devices, which are not “cleared/approved” by the FDA, there may not be a 510K or PMA number available.

- “Object of the study” question
  - When the response is “Yes”, documentation is required (usually 510k or PMA approval letter).
  - When the response is “No”, it will be the end of Section 16.
Mobile Applications

- When Should be Listed or What Should be Listed?
  - Mobile application vs Mobile Medical Application
  - Whether it meets the definition of a medical device
  - Follow most recent IRBMED’s guidance

- How should be listed?
  - See the next slides
Mobile Applications

- Section 07-2 (Special Considerations) is triggered when question 05.3 is answered “Yes” implying there will be subject interaction/recruitment/enrollment. Ensure that the below question is answered “Yes” for any health related mobile application.

![Yes No Clear](image)

Note: If there is intent to introduce the mobile medical app into commercial distribution or to publish via an app store (e.g., Google or Apple), you must contact the Office of Technology Transfer at 734-763-0614 or um-software@umich.edu to discuss licensure and U-M branding.

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Mobile Applications

When 07-2.2 is “Yes”, 07-2.2.1 will be required, which captures the intended use of the mobile app. When this is answered “Yes”, Section 16 Medical Devices will be required.

![Yes No Clear](image)

When 07-2.2.1 is answered “No”, 07-2.2.2 will open, which captures additional information about the app. Section 16 will not be triggered.

![Describe the health-related mobile software application and its intended use.](image)
### Mobile Applications

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<thead>
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- Question 07-2.2 should be “Yes”
- Question 07-2.2.1 should be “No” indicating that the app is not being used as a mobile medical app. This should be supported by the study materials (such as protocol and informed consent) as well.
- Include additional information in Question 07-2.2.2
- Section 16 is NOT required
## Mobile Applications

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End of Sections 15/16

Five most common mistakes

1. Identifying that there is an FDA regulated product
2. Completing the MIAP IND/IDE Decision Worksheet incorrectly
3. Not disclosing the investigational diagnostic tests/assays
4. Not having Section 32 (monitoring) completed
5. Not providing applicable reports or documentation to IRBMED
   - IND/IDE annual reports
   - Monitoring Reports
   - Correspondence with FDA regarding an IND/IDE
Other relevant eResearch Sections/Questions

- Question 01-2.8 Clinical Trial and Clinical Trial Phase
- Question 05.1.1 Study Protocol document (strongly recommended for FDA regulated research)
- Question 05.6 ICH GCP (mostly for drug studies)
- Question 10-1.1.1 Clinical Trial.gov
- Section 10-1. Informed Consent document
  - A statement that the study includes a investigational product
  - Risks of the drugs/devices
  - Clinicaltrial.gov language as appropriate
  - Appropriate subject injury language as applicable
- Section 32: Data Safety Monitoring
  - 32-1 AE Reporting: IRBMED Standard AE reporting plan or study-specific
  - 32-2: Data safety monitoring (monitors, DSMB, etc.)
- Section 44: Any additional supporting documents