

INVESTIGATIONAL NEW DRUG (IND) GUIDANCE

What is an IND?

An IND application is submitted to the FDA if a drug or biological product not previously authorized for marketing in the US is intended to be used for the purpose of clinical investigation, or in some cases for the purpose of clinical treatment when no other therapy is available (a treatment IND or expanded access IND).

What is the purpose of an IND?

- to ensure that the subjects will not face undue risk of harm in a clinical investigation that uses a drug, and that
- the quality of the scientific evaluation of the drug is adequate to permit the use of the investigational drug in their clinical trial (in Phase 2 and 3 studies)
- to allow for the investigational drug to be shipped lawfully for the purpose of conducting a clinical investigation

Who determines whether an IND is required?

This is determined by the PI/Sponsor, and the IRB may or may not agree with this assessment and can ask the PI to seek guidance from the FDA. Once the FDA has made the determination, the IRB accepts that determination without additional requirements.

What is an FDA regulated product?

Any drug, device, biologic, or other compound intended to affect the structure or function of the body, either approved or unapproved under the oversight of the FDA.

What is a drug?

An article (except food) intended for use in diagnosis, cure, treatment, mitigation, or prevention of disease or intended to affect the structure or function of the body. In addition to chemical compounds, this also includes biological products such as antibodies, peptides, microorganisms, vaccines and cellular therapies. A botanical product or nutritional supplement if studied for its effects on disease would be considered an investigational drug, as would an ingredient in a cosmetic (e.g. tooth whitener being tested for its ability to prevent gum disease).

When is an IND required?

An IND is required for any clinical investigation involving administration of a drug to humans unless the study is exempt from IND submission. A **clinical investigation** is defined as “an experiment in which a FDA regulated product is administered or dispensed to, or used in, one or more human subjects”. An experiment is any use of a marketed drug (approved or unapproved) except for the use of a marketed drug in the course of medical practice.

When is a clinical investigation Exempt from IND submission requirements?

The clinical investigation is Exempt from IND submission when **ALL** the following apply:

- The drug product is lawfully marketed in the US **AND**
- The investigation is not intended to be reported to FDA in support of a new indication or significant change in labeling (this type of research is usually conducted by the manufacturer, who holds the IND) **AND**
- Is not intended to support any change in advertising for prescription drugs **AND**
- The use in the study doesn't involve route of administration, dose, patient population or any other factor that significantly increases the risk associated with the use of this drug product

NOTE: Exemption criteria **only** apply to studies using a marketed pharmaceutical that is commercially available in the US, and in addition, must have IRB approval and informed consent from all participants. If only the active ingredient is used from an approved drug formulation, this is not considered a lawfully marketed product.

Exemption from IND submission?

1) Clinical investigations using an approved marketed drug

For Local Investigators initiating a study with an approved drug the investigator needs to justify why the study does not significantly increase the risk (or decreases the acceptability of the risk) associated with the use of the drug in the study. This applies if the approved drug is administered using a route of administration, dose, patient population, or other factor that is not currently approved on the package insert or in the manufacturer labeling. If the study is determined to be Exempt from IND submission, the local investigator is not considered to be a Local Sponsor Investigator

Considerations in determining whether the study significantly increases risk:

- Has the route of administration been changed?
 - A topical preparation may not be safe for oral use
 - An oral preparation is unlikely to be safe for injection, since it contains many additional ingredients used in its manufacture
- Is the dose significantly different from the approved dose?
 - If the dose of the drug is increased, there may be more adverse events experienced by the participants.
- Is the drug product use being investigated in a population that may have an increased risk with the use?
 - A drug approved for treatment in an adult population, ages 18-65, may be metabolized normally in this population, but if used in a geriatric population, metabolism may be slower, and more side effects may be seen at equivalent doses.
 - Use of a drug at the approved dose for adults may not be appropriate in a pediatric population
- Does modification of the dosage form of an approved drug change the way that the drug will be absorbed?

-Some drugs are specifically formulated such that the structure of the tablet or capsule is intended for long-term drug delivery, and crushing or breaking the tablet or emptying the contents of a capsule may alter the absorption significantly and give a much higher dose than intended in a shorter amount of time, rather than a controlled release.

-Changing the appearance of the drug, such as inserting the tablet in a capsule may not impact the way the tablet works.

2) Clinical investigations involving radio-labeled or cold isotope drugs considered safe for certain research uses after obtaining IRB approval and informed consent (and Radioactive Drug Research Committee (RDRC) approval for radio-active isotope studies)

	Radio-active isotopes		Cold isotopes	
	Exempt	Requires IND	Exempt	Requires IND
Basic Science research to obtain information regarding drug metabolism or human physiology	True	False	True	False
Not for therapeutic, diagnostic or preventive benefits for participant	True	False	True	False
Not testing for Safety and Efficacy	True	False	True	False
Dose not known to cause any clinically detectable pharmacologic effect	True	False	True	False
Radiation dose is lowest amount possible to perform the study (RDRC approval required)	True	False	N/A	N/A
Meets relevant quality standards for cold isotopes	N/A	N/A	True	False
*All scenarios listed must be conducted under IRB review with informed consent				

- **Clinical investigations of PET drugs**

PET drugs are diagnostic radiopharmaceuticals that are injected into humans to produce signals for medical imaging through the emission of a positron. Most PET drugs are produced using radionuclides generated at cyclotrons at locations close to the facility where the PET scans are performed.

- Clinical use refers to administration of the PET drug to patients as a component of their clinical care. An example of the use of a PET drug for clinical therapy would be the use of radioactive drug, 18F-FDG PET/CT in ablation therapy for thyroid cancer.
- Investigational use refers to administration of PET drugs to subjects under an IND to establish safety and/or effectiveness of a new use of the drug.
- Research use refers to the administration of a PET drug to subjects under a RDRC application, in order to obtain basic information about metabolism, physiology, pathophysiology, or biochemistry of the PET drug (not intended for therapeutic, diagnostic or safety and effectiveness information).

- **Do clinical investigations of positron emission tomography (PET) drugs need INDs?**

- An IND would generally be needed for a PET drug investigation, unless the drug is exempt from IND following the guidance in the table above.
- FDA recognizes that many PET drugs manufactured for research will not be distributed commercially, but there are still PET current good manufacturing practice (CGMP) regulations that must be adhered to for facilities that manufacture PET drugs (although the requirements that apply to research PET drug production are less stringent than those that apply to commercial facilities).
- If a PET drug used in a clinical trial is being made at a facility for which manufacturing data has been submitted in a NDA (new drug application) or an ANDA (abbreviated new drug application used for generic drugs) for the PET drug without an IND until Dec. 12, 2015, FDA has no objection to that use continuing, unless they conduct an inspection and find deficiencies in the manufacturing process.
- If manufacture at the facility began after Dec. 12, 2015, the investigational use must be covered by an IND unless the drug is exempt from all of the IND requirements.
- For example: If an ANDA for Fluodeoxyglucose F-18 (FDG F-18) has been submitted to the FDA by WI Medical Cyclotron, to make FDG F-18 and the ANDA lists the RII as a manufacturing site, then FDA does not object, and no IND is required by the RII. However, if a manufacturing site not listed on the ANDA manufactures the FDG F-18, then an IND is required.
- PET drugs which are going to be manufactured at the RII, are required to have submitted a traditional IND for use of the PET drug in research, unless the study is reviewed and approved by RDRC. The RDRC reports those studies using PET drugs to the FDA annually. RDRC does not review PET drugs under an IND, since the sponsor of the IND reports the studies under the IND to the FDA.

- **What does the RDRC approve?**

- The RDRC is responsible for reviewing basic science research protocols using radioactive drugs in humans that are subject to [21 CFR 361.1\(c\)](#) that are not being studied under an active IND.
- RDRC approval is based on:
 - appropriate limit on the radiation dose
 - appropriate limit on the pharmacologic dose
 - qualified study investigators
 - medical facility properly licensed to possess and handle radioactive materials
 - appropriate selection and consent of research subjects
 - appropriate quality of radioactive drug administered
 - sound research protocol design
 - reporting of adverse events by the investigator to the RDRC
 - approval by an appropriate Institutional Review Board (IRB)

3) Dietary Supplements used in a clinical investigation

- **What is a Dietary Supplement?**

Under the Dietary Supplement Health and Education Act of 1994 (DSHEA), a dietary supplement is defined as a product taken by mouth that is intended to supplement the diet and that contains one or

more dietary ingredients. (e.g. vitamins, minerals, amino acids, and herbs or botanicals). Federal law requires that every dietary supplement be labeled either with the term “dietary supplement” or a description of the product’s dietary ingredient, such as “herbal supplement” or “calcium supplement”. FDA monitors the labeling once the supplement is marketed for false claims and misbranding, and requires reports of any serious adverse events, but does not review these products for safety and efficacy before they are marketed.

- **When is a dietary supplement exempt from IND?**

- The only intent of the clinical investigation is to evaluate the dietary supplement’s effect on the structure or function of the body and not intended for a therapeutic purpose (i.e. when it does not meet the definition of a drug).

- **When is an IND required for a nutritional supplement?**

- The clinical investigation is intended to evaluate the dietary supplement’s ability to diagnose, cure, mitigate, treat, or prevent a disease.

4) Endogenous Compounds used in a clinical investigation

- **What is an endogenous compound?**

- A naturally occurring substance that is produced by the body which can bind to and activate receptors in the body. Examples of endogenous compounds include bradykinin, histamine, angiotensin, β -hydroxybutyrate, glucose, endorphin.

- **When is the use of an endogenous compound Exempt from IND?**

- If the endogenous compound (including those labeled with a cold isotope) is not being used for a therapeutic purpose, an IND is not required. However, if there is any intent to affect the structure or function of the body, the endogenous compound is considered to be a drug, and will need to meet the same exemption criteria that apply to any investigational drug.
- A common question is whether provocation or challenge studies in which an endogenous compound is administered to subjects to evoke a physiologic response, characterize a disease, or establish the mechanism of action are subject to IND requirements. In these cases, the endogenous compound is Exempt from IND because it is not being used for a therapeutic purpose.
- If the research involves a radiolabeled endogenous peptide and is intended to obtain basic information about the metabolism of the peptide or its role in physiology, pathophysiology, and biochemistry, and the dose is not known to cause any clinically detectable pharmacologic effect in humans, an IND is not required, but RDRC approval is required. (If the intent is for therapeutic or diagnostic use, or to test safety or effectiveness an IND is required).

5) Live Organisms used in a clinical investigation

- Examples of live organisms include viruses, bacteria and fungi
- **When does the use of live organism require an IND?**
- Administration of these organisms to study disease progression or host response to the organism (even when the challenge is not intended to be therapeutic or to affect structure or function of the body)
- Evaluation of whether colonization with a bacterial strain could treat or prevent disease in patients with a chronic immune disorder (e.g. fecal implant in ulcerative colitis)

INVESTIGATIONAL DEVICE EXEMPTION (IDE) GUIDANCE

What is a device?

An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar article, including a component part, or accessory which is:

1. Recognized in the official [National Formulary](#), the United States Pharmacopoeia or any supplement of either
2. Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease
3. Intended to affect the structure or any function of the body, and which does not achieve its primary purpose through chemical action within or on the body and which is not dependent on being metabolized to achieve its primary purpose.

NOTE: Software is not included in this definition of “device” if its function is intended for the following:

- administrative support of a health care facility,
- for maintaining or encouraging a healthy lifestyle,
- intended to serve as electronic patient records or
- intended for transferring, storing, converting formats, or displaying data and results.

How do you know if your study may require an IDE?

If you perform clinical trials using a device, you are subject to [Investigational Device Exemption \(IDE\) regulations](#) (21 CFR 812).

When is a clinical investigation a "device study"?

- If the objective of the clinical investigation is to assess the safety and/or effectiveness of a medical device, then the study is a device study, and is subject to regulatory oversight by the FDA.
- If the objective of the study is not to test safety and effectiveness of the device, then the study does not fall within the scope of the FDA regulations.

What is an IDE?

An IDE is a regulatory submission that permits clinical investigation of devices to determine the **safety and effectiveness** of the device.

How does the FDA distinguish between Clearance vs. Approval?

When a medical device is cleared, this means it has undergone a 510(k) submission, which FDA has reviewed and provided clearance for Class I and II devices are usually “cleared” by the FDA, which means

that the manufacturer can demonstrate that their product is “[substantially equivalent](#)” to another (similar) legally marketed device that already has FDA clearance or approval.

A premarket notification submission (PMN) or 510(k) is submitted to the FDA so that it can be reviewed and cleared. Once the FDA declares that the new medical device is substantially equivalent (SE) to a [predicate](#), it is “cleared”, and can be marketed and sold in the US (or shipped for research).

FDA approved means that the agency has determined that the benefits of the device outweigh the known risks for intended use. Manufacturers must submit a premarket approval (PMA) application and clinical testing results in order to get approval. FDA approval is usually mandatory to market or sell medical device products in the US that might have a significant risk of injury or illness, but are also beneficial to health. Class III devices are included in these types of products and are considered to be significant risk devices.

What is a predicate device?

A predicate device is a medical device that may be legally marketed in the US and used as a point of comparison for new medical devices seeking approval through FDA’s 510(k) premarket clearance pathway. The new device must be proven to be substantially equivalent in safety and efficacy to the predicate device in order to receive clearance. A new medical device is automatically classified as a Class III device, and must undergo premarket approval unless the manufacturer can demonstrate to FDA that the device is substantially equivalent to a predicate device.

What is a substantially equivalent (SE) device?

A device is substantially equivalent to the predicate device if:

It has the same intended use, **AND** has the same technological characteristics as the predicate

OR

It has the same intended use **AND** has different technological characteristics that do not raise different questions of [safety and effectiveness](#) **AND** the information submitted to the FDA demonstrates that the device is at least as safe and effective as the legally marketed device.

When is a 510(k) or PMN required?

- 1) When a device is marketed after May 28, 1976 for the first time, unless the device is exempt.
- 2) For a change or modification to a legally marketed device, if that [change could significantly alter its safety or effectiveness](#). The existing 510(k) holder has the burden of deciding whether or not the modification could significantly affect safety or effectiveness.

Who determines whether an IDE is required?

That depends on the risk associated with the use of the device in a study. The IDE regulations describe three types of device studies: exempt, non-significant risk (NSR), and significant risk (SR) studies.

- If the device falls into the Exempt device category no FDA submission is required

For studies that are not exempt, the sponsor (may be a local PI) is responsible for making the initial risk determination.

- For a non-significant risk study (NSR), the IRB can approve the study and document the decision in the IRB meeting minutes with the following information: a device description, reports of prior investigation (if available), subject selection criteria, and how the device will be used in the study (the protocol)
- If the study is a significant risk (SR) study, an IDE submission will be required, and FDA documentation must be supplied with the IRB application.

If the intent is to commercialize the device (usually applies to a startup company or the device manufacturer), it is the sponsor's responsibility to submit the IDE (a 510(k)) or PMA application to the FDA.

In order to determine if an IDE is required, the device will first need to be classified as a non-significant risk (NSR) or a significant risk device (SR).

How do you establish the device classification?

Establishing how the FDA regulates devices will assist in determining if the clinical investigation is Exempt from IDE.

Devices are classified according to risk as Class I, II and III devices, based on the level of control needed to provide reasonable assurance of safety and efficacy.

- Class I is low to moderate risk
- Class II is moderate to high risk (and may be general or special controls)

- General controls are regulatory requirements that apply to all medical devices, unless exempted by regulations including registration and listing of establishment and device, manufactured according to Good Manufacturing practice (GMP) and labeling the device according to the regulations.

– Special controls apply to Class II devices where general controls alone are not sufficient to assure safety and effectiveness.

- Class III is high risk (general controls and Premarket Approval (PMA))

How does the sponsor/PI determine what type of device study they are proposing?

(i) Exempt Studies

ANY of these types of studies could be Exempt from IDE submission to the FDA:

- The device was legally in commercial distribution before May 28, 1976 and has not been significantly changed or modified in design, components, method of manufacture or intended use, and the device owner has not changed. (These are considered to be preamendment devices) **OR**
- The device falls into the [FDA exempt Class I or Class II category exempt devices](#) (the Class II exempt devices are those with general controls, **not those with special controls**) **OR**

- The device is already cleared by the FDA and used as labeled and indicated **OR**
- Consumer preference testing **OR**
- Testing of a device modification that does not introduce any additional health or safety risks

(ii) Significant Risk Device Studies

If a study meets ANY of the following criteria, it is a SR device study:

- An investigational device intended as an implant **AND** presents a potential for serious risk to the health, safety or welfare of the participant; **OR**
- Use of the device is to support or sustain human life **AND** presents a potential for serious risk to the health, safety or welfare of the participant; **OR**
- Use is for 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 or welfare of the participant; **OR**
- Presents a serious risk to the health, safety or welfare of the participants

Examples:

- Evaluation of a cardiac aorta stent in a peripheral blood vessel
- Evaluation of an unapproved radiofrequency ablation device for treatment of liver tumors
- Extended wear contact lenses

(iii) Non-significant Device Studies

Studies that do not meet the definition for a SR study.

Examples:

- Most functional MRI studies
- Study of a non-invasive blood pressure measuring device
- Electroencephalography (EEG) studies
- Studies of wound dressings
- Contact lens studies (daily wear only)

What are the Major differences between SR and NSR studies?

	Follows <u>All</u> IDE regulations	Must have FDA approval before start	Follows abbreviated requirements*	Must report IRB approval to FDA	IRB acts as surrogate for FDA approval and reporting
Significant Risk	True	True	False	True	False
Non-significant risk	False**	False	True	False	True

*Investigational device labeling, IRB approval, informed consent, monitoring, records, reports, prohibits promotion (no progress or final reports need to be submitted to the FDA)

**Still required to report serious adverse events to the FDA

NOTE: If an amendment is made to a non-significant risk study that could increase the risk of the study to the participants, a submission to the FDA may be required.

What is the difference between NSR and Minimal Risk Determination?

The regulations state that minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (45 CFR 46.102(i)). A Minimal Risk study is a term used in the IRB regulations to identify certain studies that the IRB may approve through an expedited review procedure. For a device study to be eligible for expedited review, both the following must apply:

1) It must be a NSR study for which an IDE is not required **OR** the device is already cleared/approved by the FDA for marketing.

AND

2) Present no more than minimal risk to the subject

Determining if a device is a SR/NSR device is independent of the IRB's determination if the study is minimal risk or greater than minimal risk.

Are all in vitro diagnostic device studies Exempt from IDE submission?

In Vitro Diagnostic devices, include reagents, instruments and systems are used in diagnosis of disease and do not function in or on a patient. These devices are used to collect specimens, or to prepare or examine specimens (e.g. blood, serum, urine, spinal fluid, tissue samples) after they have been removed from the human body, and **are subject to the same regulations as other devices.**

In vitro diagnostic device studies (IVD), are exempt if **ALL** the following are true regarding the testing:

- non-invasive
- does not require an invasive sampling procedure that presents significant risk
- does not by design or intention introduce energy into the subject
- is not used as a diagnostic procedure without confirmation by another approved method

Is a Mobile Medical App considered a device?

FDA defines Mobile Medical Apps as a mobile app that incorporates device software functionality that meets the definition of a device and is **either** of the following:

- intended to be used as an accessory to a regulated medical device
- intended to transform a mobile platform into a regulated medical device.

FDA policies are independent of the platform that the mobile medical app runs on, are specific to the function of the app and apply to the functioning of the app on all platforms. (i.e. The platform, such as the smart phone, is not considered to be a medical device just because it runs the mobile medical app)

The same risk-based approach that applies to all medical devices applies to mobile medical apps.

FDA applies **Enforcement discretion** to some software functions that meet the definition of a device, and will not expect manufacturers to submit premarket review applications or to register and list their software with the FDA, or enforce the requirements under the FD&C Act (i.e. no IDE required).

Types of [device software functions that fall into this category](#) include those that:

- Help patients/users self-manage their disease or condition without providing specific treatment suggestions
- Automate simple tasks for health care providers

Examples of these types of apps to which FDA applies enforcement discretion are:

- software that alerts asthma users about environmental conditions
- software functions that use video and video games to motivate patients to do PT exercises at home
- software functions that use a checklist of common signs and symptoms to provide a list of possible medical conditions
- mobile apps that enable a patient or caregiver to create and send an alert or general emergency notification to first responder
- software functions that allow a user to collect (electronically or manually entered) blood pressure data and share this data through email, track and trend it, or upload it to a personal or electronic health record
- software functions that provide a surgeon with a list of recommended intraocular lens powers and recommended axis of implantation based on information entered by the MD

What is the [Breakthrough Device Designation Program \(BDD\)](#)?

This program is a voluntary program developed by the FDA to expedite review for medical devices or device-led combination products that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions. If BDD is granted by the FDA it is not a clearance for use of the device in research. The device is still required to go through the 510(k) or PMA process and submission of an IDE, but review times should be shorter.

The only types of devices eligible to register for this program are:

- 1) The device provides for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease conditions **AND**
- 2) The device must meet **at least one** of the following:
 - represents breakthrough technology **OR**
 - no approved or cleared alternatives exist **OR**
 - offers significant advantage over existing approved or cleared alternatives **OR**
 - device availability is in the best interests of the patients

This program supersedes the Expedited Access Pathway (EAP) and the Innovation Pathway.