



Start Here

Does the product you are using meet the FDA definition of a drug or biologic? **1**

Yes

Are you administering any drug or biological agent to human subjects as part of a research study? **2**

Yes

No

**STOP** No IND Exemption is required for this study.

Is the drug FDA approved? **3**

Yes

No

**STOP** An IND is required for this use.

Is the investigator the overall sponsor of the study

Yes

No

See IND application guidance **5**

The sponsor is responsible for submitting the IND

Is the drug being used according to the FDA-approved labeling? **4**

Yes

No

Does your study meet the following criteria of 21 CFR 312.2(b)(1)?  
  
(i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;  
(ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product  
(iii) The investigation is conducted in compliance with the applicable requirements for institutional review and informed consent

Does your study meet all of the following criteria of 21 CFR 312.2(b)(1) for the IRB to accept IND exemption?  
  
Are all the following statements about the study true?  
  
(1) is not intended to be reported to the FDA in support of new indication for use or significant change in the labeling of the product;  
(2) is not intended to support a significant change in the advertising for the product;  
(3) is not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product; **6**  
(4) is conducted in compliance with IRB review and informed consent regulations (See 21 C.F.R parts 50, 56) AND  
(5) is conducted in compliance with the rules against promotion of and charging for investigational drugs (See 21 C.F.R 312.7)

Yes

No

Submit request for IRB to recognize IND Exemption under 21 CFR 312. 2(b)

**STOP** Your study does not meet criteria for IND exemption. You must submit an IND application to FDA.

Unsure

If Investigator cannot determine, request FDA determination on IND **7**  
Exemption: Attach FDA Letter in INSPIR

# Footnotes

1. The FDA definition of 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 (other than food) 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.)
2. Note that an unapproved use in the course of medical practice is not a clinical investigation and does not require an IND because it involves the use in an individual patient where the primary intent is to treat the patient and not research.

*Note: If you are using a NEW COMBINATION of drugs, it is likely this will require an IND or an IND determination by FDA.*

3. FDA approval of a drug means that data on the drug's effects have been reviewed by CDER, and the drug is determined to provide benefits that outweigh its known and potential risks for the intended population.
4. FDA-approved labeling means that the company can include the information in their package insert (product label) regarding the use of the drug for that indication and includes indications, dosage and administration, contraindications, warnings and precautions, adverse reactions, drug interactions, information about use in specific populations, and other important information for healthcare providers. If the proposed use in the research does not correspond to the FDA-approved labeling, please follow the **No** pathway.
5. Please see guidance on IND Application procedures here:
  - [CLINICAL INVESTIGATOR: How do I put together an IND application?](#)
  - [Guidance for Investigational New Drug \(IND\) Application](#)
6. Meeting requirement for this *“The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product”*

This requires the investigator to submit data demonstrating why the use of the drug in the population of the research study and using the proposed dose and route will meet this criterion (see other side of page). Please note that if the request is not considered supported, the IRB will ask the investigator to obtain documentation from the FDA that an IND is NOT required. This can delay IRB approval.

If the investigator is UNSURE, please contact the CRRO, IRB or IPS (Investigational Pharmacy Services)

7. Resource model for request to FDA for IND exemption [here](#).
  - [TIP Sheet FORMAL REQUEST FOR INVESTIGATIONAL NEW DRUG APPLICATION \(IND\) EXEMPTION FROM THE FDA](#)
  - [IND Application Procedures: Exemptions from IND Requirements](#)

*“Historically, assessing whether a particular use of a drug in a clinical investigation significantly increases the risk or decreases the acceptability of the risk, compared to its approved use or uses, has been the most difficult issue in determining whether an IND is needed for a clinical investigation of a marketed drug” (21 CFR 312.2(b)(1)(iii)).*

## **Route of Administration:**

A change in the route of administration can introduce a significant new risk. For example, there could be a significant increase in risk if a marketed drug for oral administration is converted to a dosage form that is to be administered by injection or intravenous, intrathecal, or inhalation route. These other routes of administration introduce concerns with increased local concentrations, sterility, pyrogenicity, hypersensitivity (e.g., airway reactivity), variations in metabolism, and other issues not present with oral administration that can significantly increase the risk, or decrease the acceptability of the risk, associated with use of the drug.

## **Dose:**

Increases in dose, frequency, or duration of administration, compared to labeled dosing regimens, can significantly increase the risk in a study using a marketed drug. It is also possible that a decrease in dose could significantly increase risk. For example, administering a sub-therapeutic dose of an antiviral drug to study subjects could induce resistance in the subjects, thus rendering a subsequent therapeutic dose of the drug ineffective in treating the virus. The significance of changes in dose (in particular, increases in dose) can vary across therapeutic areas. For example, the cancer treatment guidance provides some latitude for conducting studies of high-dose cancer treatments without an IND because oncologists are generally familiar with the implications of high-dose regimens. In other clinical settings, use of higher doses than are recommended in labeling may be much more likely to significantly increase the risk or decrease the acceptability of the risk.

## **Patient Population:**

The acceptability of known and unknown risks can vary across different treatment populations (see § 312.2(b)(1)(iii)). The population chosen for study could be at increased risk compared to the approved use population for a variety of reasons, such as increased age, different disease or stage of disease, concomitant illness, decreased renal or hepatic function, or concomitant therapy. For example, a drug with significant toxicity can be approved for use in a population with a life-threatening or severely debilitating disease because the risk of toxicity is acceptable in that population. Use of that drug in a clinical investigation in a population that is not so ill (e.g., to evaluate the drug for prevention of disease or symptomatic relief), however, would present a different risk-benefit situation in which the known risks might not be acceptable. When use of the drug in a specific patient population decreases the acceptability of the known risks, the study would have to be conducted under an IND as required under 21 CFR part 312.”

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## **FDA Directory:**

[CDER Offices and Divisions](#)  
[Pre-IND Consultation Program](#)  
[OND Office and Division Contact Information](#)  
E-mail: [ONDCommunications@fda.hhs.gov](mailto:ONDCommunications@fda.hhs.gov)  
Phone: 301-796-0700 | Fax: 301-796-9856  
Office of New Drugs, Immediate Office - Mail Stop:  
6311, 10903 New Hampshire Avenue,  
Silver Spring, MD 20993

## **Additional references:**

[Sponsor-Investigator Frequently Asked Questions](#)