



VCU

Office of Research and Innovation

Determination of IND Exemption for Marketed Drugs

Investigational New Drug (IND) regulations ([21CFR312](#)) apply in human research studies that involve use of a drug (as defined in the [Food, Drug, and Cosmetic Act \(FD&C Act\)](#)) in a clinical investigation (as defined in [21CFR312.3](#)) unless otherwise exempt from IND requirements as described below. The following summary includes exemptions based on the IND Regulations, determinations from the [2013 FDA IND Exemption Guidance](#).

For assistance in determining the need for an IND please contact Betsy Ripley, MD, MS the VCU Clinical Research Compliance Officer at elizabeth.ripley@vcuhealth.org. Other resources regarding INDs and IDEs and flow sheets are located at go.vcu.edu/INDIDE.

Where questions still exist, sponsor-investigators are encouraged to contact the appropriate FDA review division for guidance. A template for requesting a concurrence of IND Exemption from the FDA is located at go.vcu.edu/indide.

For drug studies, an inquiry concerning the application of the IND regulations should be directed to the Chief, Project Management Staff, in the appropriate CDER review division. Organizational charts listing the CDER review divisions and their phone numbers are available on the Internet at

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/Overview/UCM166356.pdf>.

For biologics, the inquiry should be directed to the applications division of the appropriate review Office. Organizational charts listing the CBER review divisions and their phone numbers are available on the Internet at

www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm106001.htm

Note: The determination of need for an IND does not depend on whether the intent of the clinical investigation is commercial or non-commercial. Also, the number of subjects to be enrolled or the clinical condition of the subjects has no bearing on whether the study is subject to the IND regulations. A pilot study is subject to the same regulations and funding source (if any) is not a determinant. Unless a study meets one of the exemptions below, it is subject to IND regulations.

Criteria for Exemption for Clinical Investigations involving a Lawfully Marketed Drug(s) [21CFR312.2\(b\)\(1\)](#)

The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of an IND, **if all** of the following apply:

- (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 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;
- (iv) The investigation is conducted in compliance with the requirements for review by an IRB (21CFR56) and the requirements for informed consent (21CFR 50); and
- (v) The investigation is conducted in compliance with the requirements of 21CFR312.7 (Promotion and sale of investigational drugs).

Note: These criteria must be met for **every** marketed drug in your study.

Q: How do you determine whether a planned study will be used to support a new indication or other significant labeling or advertising claim?

Whether a planned clinical investigation will be used to support a new indication, other significant labeling change, or advertising claim may not always be known or apparent at the outset of the investigation. Generally, it seems reasonable to infer that the intent of any well-controlled trial of a marketed drug sponsored by the manufacturer of the drug would be to influence labeling or promotion in some way. On the other hand, the sponsor-investigator of an investigator-initiated study in an academic setting (a study designed and initiated by the investigator independent of the manufacturer) probably does not intend that his or her study of a marketed drug influence labeling or promotion, even if the sponsor-investigator is receiving some limited support from the drug's manufacturer. However, certain investigator-initiated research has the potential to influence labeling or promotion, notwithstanding the investigator's intent (e.g., a controlled trial with an endpoint representing improvement of a serious disease). Similarly, certain studies of effectiveness conducted by government agencies (e.g., National Institutes of Health, Veterans Administration) have the potential to influence labeling. FDA strongly encourages IND submissions for these types of studies so that the Agency can have an opportunity to provide advice on study design.

Q: How do you determine whether changes to a lawfully marketed dosage form increase risk?

FDA does not require that the exact same dosage, population, form described in approved labeling in order to meet the exemption category, but permits changes that **do not increase the risks or acceptability of the risks** above that presented by the use of the product according to approved labeling.

Investigators are advised to carefully consider risk implications of any conditions of use that deviate from those described in approved labeling, particularly in regard to route of administration, dose, and patient population.

- **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 sterility, pyrogenicity, hypersensitivity (e.g., airway reactivity), variations in metabolism, and other issues not present with oral administration.
- **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 possible that a decrease in dose could also significantly increase risk. For example, administering a low dose of a pure polysaccharide vaccine to study subjects can induce hypo- immunologic or non-immunologic responses in the subjects and can also induce tolerance to the vaccine, thus making subjects at risk for the infectious disease the vaccine is intended to prevent. 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 of oncologists' familiarity with the implications of high dose regimens, generally.
- **Population:** The acceptability of known and unknown risks can vary considerably across different treatment populations (see § 312.2(b)(1)(iii)). For example, a drug with significant toxicity can be approved for use in a population with 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 risks would likely not be acceptable. When the acceptability of the risk is significantly decreased, the study would have to be conducted under an IND as required under 21CFR312.

Revision History

Version1: UNK

Version2: October 3, 2017

Modified with permission from University of Kentucky ORI



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PI Name:

IRB #:

Version/Date:

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If your study involves marketed drug(s), please complete the following form and upload to your IRB protocol in the documents section. You must review the package inserts/FDA labeling for all marketed drugs in your study prior to completing this form. These package inserts/FDA labeling must also be uploaded to your protocol. If you have a formal concurrence of exemption from the FDA, you do not need to complete this form. Just upload the concurrence document to your protocol.

If your study involves a drug that is not FDA approved, do not use this form. Contact Betsy Ripley, MD, MS at elizabeth.ripley@vcuhealth.org regarding obtaining an IND.

1. What marketed drug(s) are being utilized in this study?

2. 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(s). Yes No

NOTE: If you have more than one drug you must be able to answer "YES" for all of the drugs. If any of the answers are "NO", then stop and contact Dr. Ripley at elizabeth.ripley@vcuhealth.org regarding obtaining an IND (if needed).

3. All of the drugs that are undergoing investigation are lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product(s). Yes No

NOTE: If you have more than one drug you must be able to answer "YES" for all of the drugs. If any of the answers are "NO", then stop and contact Dr. Ripley at elizabeth.ripley@vcuhealth.org regarding obtaining an IND (if needed).

4. For each drug, explain how the route of administration does not significantly increase the risks or decrease the acceptability of risks associated with the use of the drug product.

NOTE: If you cannot justify that the risks are not significantly increased or the acceptability decreased for any of the drugs, then stop and contact Dr. Ripley at elizabeth.ripley@vcuhealth.org regarding obtaining an IND (if needed).

5. For each drug, explain how the dose of administration does not significantly increase the risks or decrease the acceptability of risks associated with the use of the drug product.

NOTE: If you cannot justify that the risks are not significantly increased or the acceptability decreased for any of the drugs, then stop and contact Dr. Ripley at elizabeth.ripley@vcuhealth.org regarding obtaining an IND (if needed).

6. For each drug explain how the population receiving the drug does not significantly increase the risks or decrease the acceptability of risks associated with the use of the drug product.

NOTE: If you cannot justify that the risks are not significantly increased or the acceptability decreased for any of the drugs, then stop and contact Dr. Ripley at elizabeth.ripley@vcuhealth.org regarding obtaining an IND (if needed).

7. The investigation will be conducted in compliance with the requirements for review by an IRB (21 CFR 56) and the requirements for informed consent (21 CFR 50). Yes No

NOTE: If you have more than one drug you must be able to answer "YES" for all of the drugs. If any of the answers are "NO", then stop and contact Dr. Ripley at elizabeth.ripley@vcuhealth.org regarding obtaining an IND (if needed).

8. The investigation will be conducted in compliance with the requirements of 21CFR312.7 (Promotion and sale of investigational drugs). Yes No

NOTE: If you have more than one drug you must be able to answer "YES" for all of the drugs. If any of the answers are "NO", then stop and contact Dr. Ripley at elizabeth.ripley@vcuhealth.org regarding obtaining an IND (if needed).