

Summary of FDA Regulations on Exemption from IND Requirements

(Summary of [21CFR312](#) and [2013 FDA IND Exemption Guidance](#))

Introduction

In general, 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](#) and examples from the [2004 FDA Guidance](#) on IND exemptions for cancer treatment studies.

Where questions still exist, sponsor-investigators are encouraged to contact the appropriate FDA review division for guidance.

- 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 <https://www.fda.gov/about-fda/fda-organization-charts/fda-overview-organization-chart>.
- 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 <https://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. Unless a study meets one of the exemptions below, it is subject to IND regulations.

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).

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.

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** 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.

Exemption of Clinical Investigations involving In-Vitro Diagnostics

21CFR312.2(b)(2)

A clinical investigation of an *in vitro* diagnostic biological product is exempt from requirements of an IND, **if all** of the following apply:

- (i) The *in vitro* diagnostic biological product involving one or more of the following:
 - Blood grouping serum.
 - Reagent red blood cells.
 - Anti-human globulin.
- (ii) The diagnostic product is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure.
- (iii) The diagnostic product is shipped in compliance with 21CFR312.160.

Exemption for a Clinical Investigation involving a Placebo

21CFR312.2(b)(5)

A clinical investigation involving use of a placebo is IND exempt if the investigation does not otherwise require submission of an IND. Note: additional requirements apply for research in children/minors based on FDA Subpart D final rule.

Other Products

See [2013 FDA IND Exemption Guidance](#) for additional FAQs regarding need for an IND including dietary supplements, live organisms, radioactive drugs, bioavailability or bioequivalent studies, radiolabeled peptides, positron emission tomography (PET) drugs, attenuated microorganisms, radioisotopes, and others.

Additional resources links available at <https://www.research.uky.edu/uploads/original1160000-food-and-drug-administration-fda-resources-pdf>

Cancer Treatment Determinations

Below is additional guidance for when studies of lawfully marketed drugs or biological product, for the treatment of cancer, are exempt from the requirement of an IND application and examples of when they are not.

When does an IND application need to be submitted for studies of marketed drugs for treating cancer?

(excerpt from [2004 FDA Guidance](#))

When determining if an IND needs to be submitted to study marketed drugs for treating cancer, investigators must apply the exemption criteria listed in §312.2(b)(1)(i-v) in light of the discussion in this guidance. Planned studies may be considered exempt from the requirements of an IND if the studies involve a new use, dosage, schedule, route of administration, or new combination of marketed cancer products in a patient population with cancer and the following conditions apply:

- the studies are not intended to support FDA approval of a new indication or a significant change in the product labeling;
- the studies are not intended to support a significant change in the advertising for the product;
- investigators and their IRBs determine that based on the scientific literature and generally known clinical experience, there is no significant increase in the risk associated with the use of the drug product;
- the studies are to be conducted in compliance with IRB and informed consent regulations, pursuant to parts 50 and 56;
- the studies will not be used to promote unapproved indications, in compliance with §312.7.

EXAMPLES OF STUDIES

Refer to the [2004 FDA Guidance](#) for examples of studies are being provided to illustrate FDA's current thinking on the types of studies that the FDA considers to be exempt from IND regulation based on a risk assessment.

Source:

www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071717.pdf