

## Summary of FDA Regulations on Exemption from IND Requirements (summary of [21CFR312](#) and [2010 FDA DRAFT IND 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 [2010 Draft FDA IND 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 <http://www.fda.gov/AboutFDA/CentersOffices/OrganizationCharts/ucm135674.htm>.
- 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 <http://www.fda.gov/AboutFDA/CentersOffices/OrganizationCharts/ucm135943.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 exempt if the investigation does not otherwise require submission of an IND.

**Additional IND Exemption Determinations for Specific Types of  
Clinical Investigations Summarized From the  
[FDA 2010 DRAFT GUIDANCE](#)****Exemption for Bioavailability or Bioequivalence Studies (BA/BE)**[21CFR320.31](#)

BA/BE studies using unapproved versions of approved drugs be conducted without an IND ([21CFR320.31](#)), **if all** of the following conditions are met:

- (i) The drug product does not contain a new chemical entity (21CFR314.108), is not radioactively labeled, and is not cytotoxic.
- (ii) The dose (single dose or total daily dose) does not exceed the dose specified in the labeling of the approved version of the drug product.
- (iii) The investigation is conducted in compliance with the requirements for review by an IRB (21CFR56) and the requirements for informed consent (21CFR50).
- (iv) The sponsor meets the requirements for retention of test article samples (21CFR 320.31(d)(1)).

**Potential Exemption for Radioactive Drugs**[21CFR361.1](#)

FDA regulations (21CFR361.1) describe conditions under which radioactive drugs can be used for certain research without an IND when recognized as safe and effective for use in the research. See the [2010 FDA Guidance on Radioactive Drug Research](#) for clarification regarding what research studies may be conducted under the Radioactive Drug Research Committee (RDRC) vs. IND process.

**Exemption for Studies Using Cold Isotopes of Approved or Unapproved Drugs**

In exercising its enforcement discretion, FDA does not intend to object to clinical investigations using cold isotopes of unapproved drugs being conducted without an IND, if the following conditions are met:

- (i) The research is intended to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of a drug labeled with a cold isotope or regarding human physiology, pathophysiology, or biochemistry.

(ii) The research is not intended for immediate therapeutic, diagnostic, or preventive benefit to the study subject.

(iii) The dose to be administered is known not to cause any clinically detectable pharmacologic effect in humans based on clinical data from published literature or other valid human studies.

(iv) The quality of the cold isotope meets relevant quality standards.

(v) The research is reviewed and approved by an IRB (21CFR56) and informed consent is obtained from the research subjects (21CFR50).

### **Potential Requirement for an IND for Other Items Meeting Drug Definition**

- **Endogenous Compounds**

An IND is required for Endogenous Compounds, (i.e. histamine), when used in provocation or challenge studies to illicit a physiologic response, characterize a disease, or establish a mechanism of action. The IND is required even though the compound is not being used for a therapeutic purpose.

- **Live Organisms**

An IND is required for challenge studies in which a live organism, (e.g. bacteria, virus) is administered to subjects to study the pathogenesis of disease or the host response to the organism. The IND is required even though the organism is not intended to have a therapeutic purpose.

- **Dietary Supplements**

The IND determination for items meeting the definition of dietary supplement under the [Dietary Supplement Health and Education Act \(DSHEA\)](#) is based on the intent of the clinical investigation.

Dietary Supplements, (e.g. vitamins, minerals, amino acids, etc.), when used only to evaluate effect on structure or function of the body do not require an IND. However, if the clinical investigation is intended to evaluate the dietary supplements ability to diagnose, cure, mitigate, treat, or prevent a disease, an IND is required. This criteria also applies to products containing substances generally recognized as safe (GRAS) for use in food.

See [2010 FDA IND Guidance](#) for additional FAQs regarding need for an IND including radiolabeled peptides, positron emission tomography (PET) drugs, attenuated microorganisms, radioisotopes, and others.

**Source:**

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM229175.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?**

(a summary of [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

The following 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.

##### A. Studies That Generally Are Exempt

As noted above, of the five criteria in § 312.2(b)(1), four are not protocol related and one is protocol related. The following are examples of general categories of studies of marketed cancer drugs that would likely be exempt from IND regulation based on protocol-related issues.

1. Single-arm, phase 2 trials using marketed drugs to treat a cancer different from that indicated in the approved labeling and using doses and schedules similar to those in the marketed drug labeling are usually exempt. An exception may exist when standard

therapy in the population to be studied is very effective (e.g., is associated with a survival benefit); in that case, use of another regimen may expose patients to the risk of receiving an ineffective therapy and an IND would be necessary.

2. Phase 1 oncology trials of marketed drugs may be considered exempt if such therapy is appropriate for the patient population (i.e., if patients have residual cancer) and if there is no effective therapy (i.e., therapy producing cure or a documented increase in survival) that the patients have not yet received. It remains the investigator's responsibility to use starting doses that appear safe based on approved labeling or detailed literature reports, use incremental changes in dose or schedule, and carefully evaluate toxicity prior to dose escalation.

3. The study of new combinations of drugs would not ordinarily constitute a significant risk if these combinations have been described in the professional medical literature. Even when the regimen described in the literature does not use exactly the doses planned for study, incremental differences in doses from those described in the literature would not normally pose a significant risk and would not require an IND. Because of the danger of synergistic toxicity (i.e., enhanced effects from the combination) occurring with a new drug combination, if there are no data from the literature on its safety, the initial study of a new drug combination should ordinarily be performed under an IND.

Synergistic toxicity may be anticipated when one agent interferes with the metabolism or elimination of the other agent; when both agents target the same metabolic pathway or cellular function; or when one agent targets signaling pathways that are reasonably expected to modulate sensitivity to the other agent.

If it is determined that synergistic toxicity is likely, animal studies should be considered for determining a safe starting dose for the drug combination in humans.

4. Studies of new routes or schedules of administration not described in the approved labeling are generally exempt if there is sufficient clinical experience described in the literature documenting safety to determine that treatment is safe. On the other hand, initial experience with a new route of administration should be based on studies in animals, and an IND should be submitted.

5. Studies of high-dose therapy in cancer patients are likely to be considered exempt if the studies use adequately evaluated regimens that appear to have an acceptable therapeutic ratio for the population being studied. Similarly, phase 1 studies involving incremental changes from such well-described regimens are generally exempt.

#### B. Studies That Generally Are Not Exempt

As noted above, of the five criteria in § 312.2(b)(1), four are not protocol related and one is protocol related. The following are examples of general categories of studies of marketed cancer drugs that would likely not be exempt from IND regulation because of protocol-related issues.

1. Studies of cytotoxic drugs are normally not exempt in patients for whom cytotoxic therapy would not be considered standard therapy and would require special justification. Any use of cytotoxic agents in nonmalignant disease (e.g., rheumatoid

arthritis, multiple sclerosis) would, most likely, be considered to alter the acceptability of the risk of the agent.

2. Studies of adjuvant chemotherapy (chemotherapy given after surgery to remove cancer) are likely not exempt for the following reasons:

- If the population studied has a low risk of cancer recurring after surgery, treatment with any toxic therapy may indicate a significantly increased risk.
- If standard adjuvant therapy is available and produces a survival benefit, substitution of new therapy for standard therapy poses a significant risk that the new therapy will not produce the same survival benefit.
- If adjuvant trials are properly designed, they usually will be able to demonstrate whether the new therapy is safe and effective, and such results may lead to a marketing application. As discussed earlier, under regulations at § 312.2(b)(1), all investigations intended to support marketing of a new product indication, significant change in product labeling, or a significant change in the advertising for a product require an IND. During FDA review of INDs intended to support marketing applications, the Agency will provide feedback about the acceptability of trial design for this purpose.

3. Studies involving substitution of a new agent of unproven activity are generally not exempt in settings where standard therapy provides a cure or increase in survival. For instance, in the first-line treatment of testicular cancer, ovarian cancer, breast cancer, leukemia, and lymphoma, studies of new agents without proven efficacy would likely not be exempt. In this case, the critical judgment is whether it is ethical to withhold standard therapy while testing a new agent.

4. Studies are generally not exempt in settings where animal studies should be conducted to determine a safe starting dose or schedule. For example:

- Initial studies of a marketed drug given by a new route of administration are likely not exempt.
- Unless adequately described in the literature, initial studies of new drug combinations should usually be performed under an IND because of the possible occurrence of synergistic toxicity. As noted earlier, synergistic toxicity may be anticipated when one agent interferes with the metabolism or elimination of the other agent; when both agents target the same metabolic pathway or cellular function; or when one agent targets signaling pathways that are reasonably expected to modulate sensitivity to the other agent.
- Initial studies in humans of changes in the schedule of drug administration should generally be submitted in an IND. Some drugs have demonstrated significantly greater toxicity when given by an alternative schedule (e.g., methotrexate demonstrates much more hematologic toxicity when given by prolonged administration compared to intermittent administration).
- Initial studies of drugs intended to be chemosensitizers, radiosensitizers, or resistance modulators should generally be submitted in an IND. Animal studies

should be used to estimate the effect of the modulator on toxicity and to allow estimation of a safe starting dose in humans.

5. Studies intended to support approval of a new indication, a significant change in the product labeling, or a significant change in advertising are not exempt (§ 312.2(b)(1)(i), (ii)).

Please note: A clinical investigation is defined as “any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects... except of a marketed drug in the course of medical practice.” (21CFR312.3). If you conduct a study in which you administer a drug not approved for marketing to human subjects, and accordingly, conduct a clinical investigation. You must submit an IND for the conduct of a clinical investigation with an investigational new drug as required by 21CFR 312.20(a).

Source:

[www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071717.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071717.pdf)

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