Guidance for Industry

Investigational New Drug Applications (INDs)—Determining Whether Human Research Studies Can Be Conducted Without an IND

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

October 2010
Clinical/Medical

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist clinical investigators, sponsors, and sponsor-investigators[2] in determining whether human research studies must be conducted under an investigational new drug application (IND), as described in Title 21 of the Code of Federal Regulations, part 312 (21 CFR part 312) (the IND regulations). This guidance describes when an IND is required, specific situations in which an IND is not required, and a range of issues that, in FDA's experience, have been the source of confusion or misperceptions about the application of the IND regulations.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the FDA.

[2] The definitions in the IND regulations describe specific roles for the individual or individuals who conduct a clinical investigation and the individual or entity who has primary responsibility for and initiates the clinical investigation (the sponsor) (§ 312.3(b)). In the more common scenario, there is a commercial sponsor that has primary responsibility for and initiates the clinical investigation and multiple investigators who are responsible for the actual conduct of the investigation at their respective study sites. The term *sponsor-investigator* typically refers to an individual at an academic institution who takes responsibility for, initiates, and conducts a clinical investigation at a single site and therefore meets the definition of both a sponsor and investigator for purposes of the IND regulations (sometimes referred to as an *investigator-initiated study*).

II. BACKGROUND

FDA receives frequent inquiries from the academic research community (e.g., clinical investigators, institutional review boards (IRBs)) and the pharmaceutical industry about whether an IND should be submitted for various types of clinical research. These inquiries have addressed a range of issues concerning application of the IND requirements in part 312, for example: (1) clinical investigations using marketed drugs, (2) bioequivalence/bioavailability studies, (3) studies using radiolabeled or cold isotopes, (4) studies using dietary supplements, (5) studies using endogenous compounds, (6) pathogenesis studies using modified organisms, (7) studies using wild-type organisms in challenge models, and (8) studies that do not have a commercial purpose. Because of the number of inquiries and range of issues, FDA determined that it would be helpful to provide potential sponsors, clinical investigators, and sponsor-investigators with an overview of the IND requirements and the related issues that arise.

With certain exceptions, clinical investigations in which a drug is administered to human subjects must be conducted under an IND as required in part 312. Sections III, IV, and V of this guidance elaborate on (1) the criteria for when a study must be conducted under an IND, (2) the types of studies that involve drugs that are generally recognized as safe and effective (and therefore IND requirements do not apply) or that are exempt from the IND requirements, (3) FDA's use of enforcement discretion with respect to certain studies using cold isotopes conducted without an IND, and (4) the types of issues that have arisen concerning application of the IND requirements. This guidance also provides a process for seeking advice from FDA concerning the application of the IND regulations to a planned clinical investigation.

III. RESEARCH STUDIES THAT REQUIRE AN IND

In general, the IND regulations in part 312 require that human research studies be conducted under an IND if all of the following conditions exist:

- The research involves a *drug* as that term is defined in section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 321(g)(1)).

- The research is a *clinical investigation* as defined in the IND regulations (21 CFR 312.3).

- The clinical investigation is not otherwise *exempt* from the IND requirements in part 312 (see section IV of this guidance).

A. What Is a Drug?

The definition of the term *drug* in section 201(g)(1) of the FD&C Act includes, among other things, "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease . . ." and "articles (other than food) intended to affect the structure or any function of the body of man or other animals." Biological products subject to licensure under section 351 of the Public Health Service Act (42 U.S.C. 262) may also be considered drugs within the meaning of the FD&C Act. It is important to note that the *drug* definition is not limited to compounds

intended for a therapeutic purpose.[3] The definition also includes compounds intended to affect the structure or function of the body, without regard to whether the compound is intended to influence a disease process. For example, the definition includes compounds administered to healthy subjects to blunt or provoke a physiologic response or to study the mechanism of action or metabolism of a drug. Note, however, that a dietary supplement (as defined in section VI.C) intended only to affect the structure or function of the body and not intended for a therapeutic purpose is not a drug.

B. What Is a Clinical Investigation?

The IND regulations in § 312.3(b) define *clinical investigation*[4] as:

> . . . [an] experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of [the IND regulations], an experiment is any use of a drug [whether approved or unapproved] except for the use of a marketed drug in the course of medical practice.

In contrast, use of a lawfully marketed drug in the course of medical practice involves the use in an individual patient where the primary intent is to treat the patient but not to study the safety or effectiveness of a drug in any systematic way. For example, FDA considers use of a lawfully marketed drug in a randomized trial to be a clinical investigation.

IV. CLINICAL INVESTIGATIONS INVOLVING DRUGS GENERALLY RECOGNIZED AS SAFE AND EFFECTIVE AND CLINICAL INVESTIGATIONS EXEMPT FROM THE IND REQUIREMENTS BY REGULATION

FDA regulations describe three categories of clinical investigations that are exempt from the IND requirements in part 312 or to which the IND requirements are not applicable (i.e., an IND submission is not needed for these clinical investigations), provided the criteria are met (see 21 CFR 312.2(b), 320.31(b), and 361.1). The three categories of clinical investigations and the applicable criteria are listed in the following subsections. Ordinarily, clinical investigations that do not meet these criteria must be conducted under an IND as required in part 312.

A. Certain Research Involving Marketed Drug Products

A clinical investigation of a drug is exempt from the IND requirements if all of the criteria for an exemption in § 312.2(b) are met:

- The drug product is lawfully marketed in the United States.

[3] In this guidance, the term *therapeutic purpose* is intended to encompass diagnosis, cure, mitigation, treatment, and prevention of disease.

[4] Additional information on clinical investigations is available on the FDA Web site at http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm.

- There is no intent to report the investigation to FDA as a well-controlled study in support of a new indication and no intent to use it to support any other significant change in the labeling of the drug.

- In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.

- The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2(b)(1)(iii)).

- The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50).

- The investigation is conducted in compliance with the requirements of § 312.7 (i.e., the investigation is not intended to promote or commercialize the drug product).

The party planning to conduct a clinical investigation using a marketed drug is responsible for determining whether the planned study meets the criteria for an exemption.[5] The exemption regulation does, however, provide a mechanism for clinical investigators or potential sponsors to seek advice from FDA on the applicability of the IND regulations to a planned clinical investigation if there is uncertainty about such applicability (§ 312.2(e)).

Three of the criteria for exemption listed previously merit further discussion.

- What is meant by a *drug product that is lawfully marketed in the United States*?

  The preamble to the final rule incorporating the IND exemption criteria into the IND regulations makes clear that the exemption provision was not intended to require use of only the marketed version of the drug product for a clinical investigation to be exempt from the IND requirements. The intent was to provide some latitude to modify the marketed version of the drug product for use in a clinical investigation. In responding to comments asking FDA to clarify to what extent a sponsor could change the marketed drug product or conditions of use and still be exempt from the IND regulations, FDA stated that:

  > The exemption was not intended to require an investigator to use the drug in exactly the same dosage form, dosage levels, and patient populations

[5] The preamble to the rule finalizing the IND regulations provides:

> FDA recognizes that a considerable amount of professional judgment must be exercised in determining whether the conditions of an investigation "significantly increase" the risk associated with use of the drug. Because the assessment of risks involved in a therapeutic procedure is an everyday part of the practice of medicine, the individual investigator should usually be able to determine the applicability of the exemption.

(See the final rule on New Drug, Antibiotic, and Biologic Drug Product Regulations that published in the *Federal Register* of March 19, 1987 (52 FR 8798)).

> described in the marketed labeling for the product, but rather to permit changes to the lawfully marketed drug product that do not increase the risks . . . over the risk presented by use of the product in conformance with its marketed labeling.[6]

Therefore, sponsors or sponsor-investigators can make low-risk modifications to the lawfully marketed dosage form to, for example, blind a study.

In making modifications to the marketed dosage form, sponsors and sponsor-investigators should consider the potential risk implications of the modifications based on the type and complexity of the dosage form. For example, minor variations to solid oral dosage forms, such as changing the color, scoring, or capsule size of the marketed dosage form for blinding purposes, would generally be low risk provided the changes did not involve major manufacturing or formulation changes. Similarly, using capsules to over-encapsulate the marketed dosage form would generally be low risk provided the capsule meets appropriate standards. Changes to more complex oral dosage forms and injectable and other non-oral dosage forms would usually carry greater risk. Products that are very sensitive to conditions in their environment (e.g., protein products) also carry greater risk because changes to the formulation, dosage form, manufacturing, or primary packaging may significantly increase risk for such products.

Given the range of possible modifications to a marketed dosage form, FDA cannot provide comprehensive guidance on the degree of risk presented by all such modifications. If sponsors or sponsor-investigators have concerns about whether changes to a lawfully marketed dosage form increase risk to an extent that an IND would be required, they should consult FDA (see section VIII). We recommend they provide FDA with a listing of chemistry, manufacturing, and controls (CMC) variations from the marketed version of the drug product, if CMC information for the marketed product is available to them, and any other pertinent information that would assist FDA in responding to an inquiry.

- Is the risk associated with the product significantly increased (or the acceptability of the risk significantly decreased)?

  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)). This provision has been particularly difficult in the oncology setting where many of the therapies have significant toxicity, and for that reason, FDA has issued guidance to help clinical investigators studying cancer treatments to determine whether the risk associated with the use of the drug in a planned clinical investigation is significantly increased, or

[6] Final rule, "New Drug, Antibiotic, and Biologic Drug Product Regulations" (52 FR 8798 at 8801, March 19, 1987).

the acceptability of the risk is significantly decreased.[7] FDA's cancer treatment guidance is also a useful reference for clinical studies of marketed drugs in other therapeutic areas, particularly for studies in other serious and life-threatening conditions, as the risk-benefit scenarios are at least somewhat relevant to non-oncologic settings. Investigators should carefully consider the risk implications of any conditions of use in the study that deviate from the conditions of use described in the drug's labeling, with particular attention to the following:

- 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.

- Patient 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 21 CFR part 312.

[7] See the guidance for industry, *IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer* (the cancer treatment guidance). We update guidances periodically. To make sure you have the most recent version of a guidance, check the Drugs guidance page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm and the Biologics guidance page at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

- Does the sponsor intend to (1) report the investigation to FDA as a well-controlled study in support of a new indication, (2) use it to support any other significant change in the labeling of the drug, or (3) use it to support a significant change in the advertising (for prescription drugs only) for the drug?

  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.

B. Bioavailability or Bioequivalence Studies in Humans

FDA regulations describe criteria under which bioavailability or bioequivalence (BA/BE) studies using unapproved versions of approved drug products can be conducted without submission of an IND (21 CFR 320.31(b) and (d)). Although these regulations are intended to facilitate development of generic drugs, a planned BA/BE study need not be intended for that purpose to be exempt from the IND regulations. A BA/BE study in humans does not require an IND if all of the following conditions are met:

- The drug product does not contain a new chemical entity (21 CFR 314.108), is not radioactively labeled, and is not cytotoxic.

- 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.

- The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and the requirements for informed consent (21 CFR part 50).

- The sponsor meets the requirements for retention of test article samples (21 CFR 320.31(d)(1)).

C. Radioactive Drugs for Certain Research Uses

FDA regulations (21 CFR 361.1) describe conditions under which radioactive drugs (drugs containing unstable isotopes) can be used for certain research without an IND because they are generally recognized as safe and effective for those uses. These regulations apply to radioactive versions of both approved and unapproved drugs.[8]

V. CLINICAL INVESTIGATIONS USING COLD ISOTOPES

Cold isotopes (isotopes that lack radioactivity) have been increasingly used for the same research purposes as radioactive isotopes—to obtain basic information about drug metabolism or about human physiology, pathophysiology, or biochemistry. When used for these basic research purposes, cold (or stable) isotopes ordinarily present fewer safety concerns than radioactive isotopes. Unlike radioactive isotopes, however, there is no specific regulation analogous to 21 CFR 361.1 that addresses cold isotopes of approved drugs and unapproved drugs when used for these basic research purposes (see discussion of radioactive isotopes in section IV.C). However, FDA believes there is no need to have more stringent requirements for studies that use cold isotopes than for those that use radioactive isotopes, and historically, FDA has not objected to studies using cold isotopes being conducted without an IND. 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, provided the following conditions are met (the conditions are based on the criteria for studies using radiolabeled drugs (see 21 CFR 361.1)):[9]

- 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.

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

- 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.

- The quality of the cold isotope meets relevant quality standards.

[8] For information on determining whether human research with a radioactive drug can be conducted under a Radioactive Drug Research Committee (RDRC), see FDA's draft guidance for industry and researchers, *The Radioactive Drug Research Committee: Human Research Without an Investigational New Drug Application* (the RDRC guidance), issued June 2009, available on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. This draft guidance, when finalized, will provide recommendations on this topic.

[9] Note that studies using cold isotopes of approved drugs would routinely meet the criteria for exemption from the IND requirements in part 312 for studies of marketed drugs (see section IV.A) because the studies involve such low doses and thus present low risk. Therefore, enforcement discretion is not needed for these studies to be conducted without an IND.

- The research is reviewed and approved by an IRB (21 CFR part 56) and informed consent is obtained from the research subjects (21 CFR part 50).

VI. SPECIFIC ISSUES CONCERNING THE APPLICATION OF THE IND REGULATIONS

This section addresses certain issues that frequently arise in discussions with outside parties concerning the application of the IND requirements in 21 CFR part 312.

A. Endogenous Compounds

FDA has received numerous questions concerning the application of the IND requirements to studies in which endogenous compounds are administered to human subjects. A common question is whether *provocation* or *challenge* studies in which an endogenous compound (e.g., bradykinin, histamine, angiotensin) 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 plainly not being used for a therapeutic purpose. There is, however, intent to affect the structure or function of the body, so the compound would be considered a drug. Therefore, these types of studies are clinical investigations and require an IND under part 312, unless they meet the criteria for an exemption in §§ 312.2(b), 320.31(b), or the criteria in § 361.1 (see section IV) or the endogenous compound is labeled with a cold isotope and used in the manner described in section V.

B. Live Organisms

An IND is required for challenge studies in which a live organism (e.g., virus, bacteria, or fungi that is modified or wild-type) is administered to subjects to study the pathogenesis of disease or the host response to the organism (see part 312). Although the challenge organism is not intended to have a therapeutic purpose, there is intent to affect the structure or function of the body. Thus, the organism is a biological product (see 21 CFR 600.3(h)(1)) and a drug, and an IND is required for the clinical investigation, unless the criteria for exemption in 21 CFR 312.2 are met. Similarly, an IND is required for a clinical investigation designed to evaluate whether a product colonized with a strain of bacteria and then administered to subjects can treat or prevent disease in patients with a chronic immune disorder.

C. Dietary Supplements

Under the Dietary Supplement Health and Education Act (DSHEA) of 1994, a dietary supplement is defined, in part, as a product taken by mouth that is intended to supplement the diet and that contains a dietary ingredient.[10] The dietary ingredients in these products can include vitamins, minerals, herbs and other botanicals, amino acids, other dietary substances intended to supplement the diet, and concentrates, metabolites, constituents, extracts, or combinations of the preceding types of ingredients. Dietary supplements can be found in many forms such as tablets, capsules, softgels, liquids, or powders.

[10] See section 201(ff) of the FD&C Act (21 U.S.C. 321(ff)).

Under DSHEA, a dietary supplement is not considered a drug and is not subject to the premarket approval requirements for drugs if the intended use for which it is marketed is only to affect the structure or any function of the body (i.e., not intended to be used for a therapeutic purpose). Similarly, whether an IND is needed for a clinical investigation evaluating a dietary supplement is determined by the intent of the clinical investigation. If the clinical investigation is intended only to evaluate the dietary supplement's effect on the structure or function of the body, an IND is not required.

However, if the clinical investigation is intended to evaluate the dietary supplement's ability to diagnose, cure, mitigate, treat, or prevent a disease,[11] an IND is required under part 312. For example, a clinical investigation designed to study the relationship between a dietary supplement's effect on normal structure or function in humans (e.g., calcium and bone mass) or to characterize the mechanism by which a dietary supplement acts to maintain such structure or function (e.g., fiber and bowel regularity) would not need to be conducted under an IND. However, a clinical investigation designed to evaluate a dietary supplement's ability to prevent osteoporosis or to treat diarrhea or constipation would need to be conducted under an IND under part 312.

D. Research with Noncommercial Intent

There seems to be a belief among some investigators and IRBs that the IND regulations do not apply to clinical investigations that are not intended to investigate a drug's potential for commercial sale. This belief is not correct. Whether the IND regulations apply to a planned clinical investigation does not depend on whether the intent of the clinical investigation is commercial or noncommercial. Therefore, these types of studies would require an IND under part 312, unless they meet the criteria for an exemption in §§ 312.2(b), 320.31(b), or the criteria in § 361.1 (see section IV) or the compound used is labeled with a cold isotope and used in the manner described in section V.

VII. FREQUENTLY ASKED QUESTIONS

1. Do I need an IND if I use a lawfully marketed drug for an unlabeled indication?

If you prescribe a marketed drug to treat a patient for an unlabeled indication (also referred to as *off-label* use), an IND is not required because this use is considered to be within the scope of medical practice and not a clinical investigation. However, if you use the marketed drug for the same purpose in a clinical investigation intended to evaluate the drug's ability to treat a disease or condition, an IND is required under part 312 unless the clinical investigation meets the criteria for an exemption for studies of lawfully marketed drugs in § CFR 312.2(b) (see section IV.A).

[11] For purposes of the dietary supplement labeling requirements, a "'disease' is damage to an organ, part, structure, or system of the body such that it does not function properly (e.g., cardiovascular disease), or a state of health leading to such dysfunctioning (e.g., hypertension); except that diseases resulting from essential nutrient deficiencies (e.g., scurvy, pellagra) are not included in this definition" (21 CFR 101.93(g)).

2. If a drug marketed for use in adults is studied in an investigator-initiated, single-center study involving children, is an IND needed?

An IND is required under part 312 unless the clinical investigation meets the criteria for an exemption in § 312.2(b) (see section IV.A). The criterion of most importance for the exemption in this situation is whether the change in study population from adult to pediatric, or any other condition of use in the study, would significantly increase the risks (or decrease the acceptability of the risks) associated with the use of the drug (21 CFR 312.2(b)(1)(iii)). Whether risk would be significantly increased would depend on a variety factors, including, for example, the age of the pediatric population being studied, the extent of prior pediatric experience with the drug in clinical studies or clinical practice, the amount of information available to support dosing in the study population, and the overall toxicity profile of the drug.

3. There are drugs on the market that have not been approved by FDA. Do clinical investigations using those drugs need an IND?

There are certain currently marketed drug ingredients that were first marketed before Congress passed the FD&C Act of 1938 (requiring demonstration of safety before marketing) or before it passed the 1962 amendments to the FD&C Act (requiring demonstration of effectiveness and safety before marketing). Sponsors of clinical investigations that use products with these ingredients should consult with FDA about the need for an IND under part 312.

4. Can I do research on radiolabeled endogenous peptides, such as neuropeptides, without an IND?

If the research is intended to obtain basic information about the metabolism of the peptide or its role in physiology, pathophysiology, and biochemistry, and the criteria in 21 CFR 361.1 are met (i.e., among other things, the dose of endogenous peptide to be administered is known not to cause a clinically detectable pharmacologic effect in humans), then an IND is not required (see the RDRC guidance). However, if the study hypothesis concerns the diagnosis, cure, mitigation, treatment, or prevention of a disease in patients, or the criteria in § 361.1 are otherwise not met, an IND is required under part 312.

5. Do clinical investigations of positron emission tomography (PET) drugs need INDs?

Normally, an IND is required unless a PET drug investigation meets the criteria in 21 CFR 361.1 The research must be intended to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of a radioactively labeled drug or regarding human physiology, pathophysiology, or biochemistry, but not intended for immediate therapeutic, diagnostic, or similar purposes or to determine the safety and effectiveness of the drug in humans for such purposes (i.e., to carry out a clinical trial) (21 CFR 361.1(a)).

6. *If a complementary or alternative medicine that was derived from organic materials from a botanical source (e.g., broccoli, sprouts) is administered to subjects to study cancer prevention, is an IND required?*

   A clinical investigation of a complementary or alternative medicine derived from organic materials that is intended to evaluate the medicine's ability to diagnose, cure, mitigate, treat, or prevent disease requires an IND under part 312.[12]

7. *Is an IND required if a product containing attenuated microorganisms is evaluated for amelioration of symptoms of a disease or prevention of the disease?*

   Even when a microorganism is attenuated with the intention to increase safety of a product, a clinical investigation that evaluates the potential for that microorganism to relieve symptoms of a disease or prevent the disease requires an IND under part 312, unless the study meets the criteria for an exemption under 21 CFR 312.2(b).

8. *If a product containing substances generally recognized as safe (GRAS) for use in food is administered to subjects in a study intended to evaluate the effect of the substance on the pathogenesis of a human disease, is an IND required?*

   Substances designated as GRAS for use in food are not approved as drug products. A clinical investigation of a GRAS substance that is intended to evaluate the product's ability to diagnose, cure, mitigate, treat, or prevent disease requires an IND under part 312, unless the substance to be studied is also a lawfully marketed drug and the clinical investigation meets the criteria for exemption under 21 CFR 312.2(b).

9. *For purposes of the exemption from the IND requirements for studies using radioisotopes and FDA's exercise of enforcement discretion for studies using cold isotopes, what support is needed to determine that the labeled drug does not have a clinically detectable pharmacological effect?*

   There is no requirement for a formal dose-response study to define the lower threshold for a clinically detectable pharmacological effect, and in some cases a study may not be needed. For example, if the labeled drug is an endogenous compound and the circulating blood levels or excretion rates of the endogenously produced substance are well known, there could be a basis to conclude that some small fraction of these levels or rates of administration (e.g., administration over a given interval of a very low percentage of the amount of a substance that is produced endogenously during the same interval) represents an amount without detectable pharmacological effect. Similarly, if large amounts of a substance such as an amino acid or a sugar are regularly consumed as foodstuffs, it may be possible to conclude that consumption of a small amount of these substances (e.g., a small percentage of the amount usually consumed during a meal), at least by the oral route, would be without detectable pharmacological activity (also see footnote 8).

[12] See the guidance for industry on *Botanical Drug Products*, available on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

10. Do I need an IND if my study uses a home-made *version of a lawfully marketed drug?*

Some investigators, or research pharmacies affiliated with the institution in which an investigator is conducting a study, compound their own versions of lawfully marketed drug products for use in clinical studies. For example, FDA is aware of instances in which the methacholine used in respiratory studies for challenge purposes has been prepared locally from raw materials obtained from a chemical supply company. Studies that use a drug product that is prepared from raw materials by, or at the behest of, the sponsor or investigator in place of the approved, finished product marketed by its manufacturer must be conducted under an IND (21 CFR part 312). These studies cannot meet the criteria for an exemption from the IND requirements for marketed drugs (§ 312.2(b)) because the drug product manufactured by the investigator or research pharmacy is not considered to be the lawfully marketed drug, nor is the drug product generally recognized as safe and effective, in which case the IND requirements do not apply (§ 361.1).

11. Do I need an IND if my study enrolls only a small number of subjects?

The number of subjects enrolled has no bearing on whether the study is subject to the IND regulations. The definition of *clinical investigation* specifically includes studies with as few as one subject (see section III.B).

12. Do I need an IND if my study enrolls only healthy volunteers?

The clinical condition of study subjects (e.g., the presence or absence of disease) has no bearing on whether the study is subject to the IND requirements in part 312. The definition of *clinical investigation* refers only to subjects involved in an experiment. It makes no distinction between healthy subjects or those with a disease (see section III.B).

VIII. PROCESS FOR ADDRESSING INQUIRIES CONCERNING THE APPLICATION OF THE IND REQUIREMENTS

The sponsor (or sponsor-investigator of an individual investigator-initiated study) should be able to determine whether the IND regulations apply to a planned clinical investigation as required under 21 CFR 312.2(a). If a sponsor is uncertain, however, we recommend that the sponsor contact the appropriate review division (i.e., for the therapeutic area being studied) in the appropriate center for advice about whether the IND regulations apply (21 CFR 312.2(e)). For products regulated by CDER, an inquiry concerning the application of the IND regulations should be directed to the Chief, Project Management Staff, in the appropriate CDER review division. For products regulated by CBER, the inquiry should be directed to the applications division of the appropriate review Office.

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. 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. If the relevant review division is not known, we

recommend the sponsor contact CDER's Division of Drug Information or CBER's Division of Manufacturer's Assistance and Training (matt@cber.fda.gov), Office of Communication, Outreach and Development (both addresses and phone numbers are provided on the second title page of this guidance).

FDA will categorize inquiries concerning the application of the IND regulations as either informal or formal based on the following factors:

- The medium in which the inquiry is received
- The relative complexity of the inquiry
- The type of response requested by the inquirer or given by FDA

Informal inquiries have the following features:

- They can be communicated either orally or in writing (written communication includes e-mail, fax, or other written correspondence).
- They can pose only relatively uncomplicated questions about a planned clinical investigation that FDA can answer based on somewhat limited information.
- The inquirer is not seeking a formal written response.

In response to an inquiry intended to be informal, FDA can (1) provide an informal (qualified, nonbinding) response, either orally or in writing, concerning the applicability of the IND regulations based on its understanding of the planned clinical investigation; (2) ask for additional information before providing an informal response; or (3) determine that the inquiry poses a complex question that should be submitted as a formal inquiry. FDA will not retain and track informal responses to inquiries concerning the applicability of the IND regulations to planned clinical investigations.

Formal inquiries have all of the following features:

- They are in writing (can be paper or electronic).
- They can pose a question of any level of complexity.
- The inquirer is seeking a formal written response or FDA determines that a formal written response should be given (i.e., that the inquiry cannot be answered informally).
- The documentation contains enough detail to permit FDA to provide a formal response concerning the applicability of the IND regulations to a planned clinical investigation (e.g., a study protocol, information about the drug product).

In response to a formal inquiry, FDA may provide a formal written response concerning the application of the IND requirements (part 312) to a planned clinical investigation or may determine that it has insufficient information to provide a formal response and seek additional

information before providing a response. The scope of any formal response would be limited to the conduct of a clinical investigation consistent with the investigation described in documentation provided to FDA. If there are significant changes to the protocol or other aspects of the planned investigation after FDA has provided a response, that response may no longer be valid. FDA will track formal inquiries.

APPENDIX

Other Guidances That May Be Relevant to Questions Concerning the Application of the IND Requirements

FDA has issued guidances in related areas. Interested persons may wish to refer to the following documents, available on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm:

- Guidance for industry on *Botanical Drug Products*, which includes guidance on submitting INDs for botanical drug products, including those botanical products currently lawfully marketed as foods (including conventional foods and dietary supplements) in the United States.

- Guidance for industry, investigators, and reviewers on *Exploratory IND Studies*, which is intended to clarify what preclinical and clinical approaches, as well as chemistry, manufacturing, and controls information, should be considered when planning exploratory studies in humans, including studies of closely related drugs or therapeutic biological products, under an IND.

- Draft guidance for industry on *INDs--Approaches to Complying with CGMP During Phase 1*, issued January 2006. When finalized, this guidance will provide recommendations on this topic.

- Draft guidance for industry, *Complementary and Alternative Medicine Products and Their Regulation by the Food and Drug Administration*, issued December 2006. When finalized, this guidance will provide recommendations on this topic.

- Draft guidance for industry and researchers, *The Radioactive Drug Research Committee: Human Research Without an Investigational New Drug Application*, issued June 2009. When finalized, this guidance will clarify whether research using a radioactive drug must be conducted under an IND (21 CFR part 312), may be exempt from IND requirements (21 CFR 312.2(b)), or if certain conditions are met, can be conducted under the supervision and approval of an FDA-approved Radioactive Drug Research Committee (21 CFR 361.1) without an IND. In addition, FDA has established a Web site at http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Oncology/default.htm for easy access to information by IRBs, clinical investigators, sponsors, and others.