NOTE: A stay is in effect for parts of subsection VI.D of this guidance. Additional information about this stay can be found in the Notice of Stay that published in the *Federal Register* of October 30, 2015 (80 FR 66907).

Guidance for Clinical Investigators, Sponsors, and IRBs

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

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)
Center for Food Safety and Applied Nutrition (CFSAN)

September 2013
Clinical/Medical

Guidance for Clinical Investigators, Sponsors, and IRBs

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

Additional copies are available from:

Office of Communications,
Division of Drug Information, WO 51, Room 2201
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Rockville, MD 20993-0002
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

and/or
Office of Communication, Outreach and
Development, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
Phone: 800-835-4709 or 301-827-1800
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

and/or
Outreach and Information Center
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740
Phone: 888-723-3366
http://www.fda.gov/Food/GuidanceRegulation/default.htm

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)
Center for Food Safety and Applied Nutrition (CFSAN)

September 2013
Clinical/Medical

TABLE OF CONTENTS

[†] Part of this subsection is stayed.

Contains Nonbinding Recommendations

Guidance for Clinical Investigators, Sponsors, and IRBs[1]

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

This guidance represents 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, sponsor-investigators,[2] and institutional review boards (IRBs) in determining whether research studies involving human subjects 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.[3] This guidance addresses only whether an IND is needed. If your study also involves the use of a device, you should determine whether such use is subject to 21 CFR part 812 (the IDE 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

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Food Safety and Applied Nutrition (CFSAN) at the Food and Drug Administration (FDA or the Agency).

[2] The definitions in the IND regulations describe specific roles for the individual or individuals who conduct a clinical investigation (the investigators) and the individual or entity who has primary responsibility for and initiates the clinical investigation (the sponsor) (§ 312.3(b)). In the most common scenario, a commercial sponsor has primary responsibility for and initiates the clinical investigation, and multiple investigators 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 (sometimes referred to as an *investigator-initiated study*) and therefore meets the definition of both a sponsor and an investigator for purposes of the IND regulations.

[3] This guidance does not address expanded access to investigational drugs for treatment use under subpart I of 21 CFR part 312.

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.

II. BACKGROUND

FDA has two primary objectives in reviewing an IND: (1) to assure the safety and rights of subjects in all phases of an investigation and (2) in phases 2 and 3, to help assure that the quality of the scientific evaluation of the drug is adequate to permit an evaluation of the drug's effectiveness and safety (21 CFR 312.22).

FDA receives frequent inquiries from the academic community (e.g., clinical investigators, IRBs) and the pharmaceutical industry about whether an IND should be submitted for various types of clinical research. Inquiries have related to a range of issues concerning application of the IND requirements in part 312, including, for example:

- Clinical investigations using marketed drugs
- Bioequivalence/bioavailability studies
- Studies using radiolabeled or cold isotopes
- Studies using dietary supplements or foods
- Studies using endogenous compounds
- Pathogenesis studies using modified organisms
- Studies using wild-type organisms in challenge models
- Studies that do not have a commercial purpose

Because of the large number of inquiries and wide range of issues, FDA determined that it would be helpful to provide to potential sponsors, clinical investigators, and sponsor-investigators an overview of the IND requirements and related issues.

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 the criteria for when a study must be conducted under an IND; the types of studies that involve drugs, but that are exempt from the IND requirements; studies involving radioactive drugs that are generally recognized as safe and effective (and to which IND requirements therefore do not apply); and FDA's use of enforcement discretion with respect to certain studies using cold isotopes conducted without an IND. Section VI discusses specific issues that frequently arise concerning application of the IND regulations; section VII contains frequently asked questions; and section VIII describes the 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. A *biological product* is:

> . . . a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.

(42 U.S.C. 262(i))

Biological products include, among other products, bacterial vaccines, allergenic extracts, gene therapy products, growth factors, cytokines, and monoclonal antibodies.

It is important to note that the *drug* definition is not limited to compounds intended for a therapeutic purpose.[4] 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 individuals to prevent pregnancy or treat male pattern baldness. The definition also includes compounds used for research purposes in healthy subjects to blunt or provoke a physiologic response or study the mechanism of action or metabolism of a drug (see section VI.A). Note, however, that (1) a dietary supplement intended only to affect the structure or function of the body and not intended for a therapeutic purpose is not a drug[5] (see section VI.D.1) and (2) a food used as such (i.e., primarily for its taste, aroma, or nutritive value) and not for a therapeutic purpose or to affect the structure or function of the body, other than by providing nutrition, is not a drug (see section VI.D.2).[6]

---

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

[5] See 21 CFR 101.93(f) and (g); 65 FR 1000 (Jan. 6, 2000).

[6] See 21 U.S.C. 321(f) and (g)(1); *Nutrilab v. Schweiker*, 713 F.2d 335 (7th Cir. 1983)).

B. What Is a Clinical Investigation?

The IND regulations in § 312.3(b) define *clinical investigation*[7] 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.

For example, a randomized trial evaluating an unapproved use of a lawfully marketed drug is a clinical investigation and may require an IND.[8] In contrast, use of a lawfully marketed drug for 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.

IV. CLINICAL INVESTIGATIONS THAT ARE EXEMPT FROM THE IND REQUIREMENTS BY REGULATION

FDA regulations describe two categories of clinical investigations that are exempt from the IND requirements in part 312, provided the criteria for exemption are met (see 21 CFR 312.2(b) and 320.31(b)). The two categories of clinical investigations and the applicable criteria are described in the following subsections. Ordinarily, clinical investigations of drugs that do not meet these criteria must be conducted under an IND as required in part 312.

A. Certain Research Involving Marketed Drug Products

Whether an IND is needed to conduct a clinical investigation of a marketed drug primarily depends on the intent of the investigation and the degree of risk associated with the use of the drug in the investigation. A clinical investigation of a *marketed* 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.
- The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is 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)).

[7] Additional information on clinical investigations is available on FDA's Web site at http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm.
[8] See section IV.A of this guidance.

- 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 potential sponsor or sponsor-investigator of a planned clinical investigation using a marketed drug is responsible for determining whether the investigation meets the criteria for an exemption.[9] If there is uncertainty about whether the exemption criteria are met, the potential sponsor or sponsor-investigator can seek advice from FDA on the applicability of the IND regulations (§ 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 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.[10]

  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,

[9] 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 at 8802)).

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

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 met appropriate standards. Changes to more complex oral dosage forms and injectable and other non-oral dosage forms might 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 might change the pharmacokinetics, immunogenicity, or other characteristics of 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). If a sponsor or sponsor-investigator consults FDA, they should 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; for that reason, FDA has issued guidance to help clinical investigators studying cancer treatments determine whether the risk associated with the use of the drug in a planned clinical investigation is significantly increased or the acceptability of the risk is significantly decreased.[11] 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:

[11] 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.

- 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.

- Does the sponsor intend to (1) report to FDA the investigation 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?

Generally, it seems reasonable to infer that any well-controlled trial of a marketed drug (e.g., a study of a new indication) sponsored by the manufacturer of the drug would be intended to be used to influence labeling or promotion in some significant way and would have to be conducted under an IND. On the other hand, similar studies of marketed drugs conducted by an entity that

does not have an independent ability to change a drug's labeling – e.g., a study conducted by a sponsor-investigator in an academic setting or Government agency sponsor – would not generally be intended to be submitted to FDA to support a new indication or to otherwise influence the drug's labeling or promotion. However, data from such studies may subsequently be submitted to FDA for that purpose and, therefore, FDA has an interest in helping to ensure that these studies are designed to yield data adequate to support a labeling change. A sponsor who would like to obtain FDA advice on study design can submit an IND for FDA review.

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 with 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)) and safety reporting (21 CFR 320.31(d)(3)).

V. HUMAN RESEARCH STUDIES INVOLVING RADIOACTIVE OR COLD ISOTOPES

A. Radioactive Isotopes

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.[12]

Under 21 CFR part 361, human research using a radioactive drug or biological product may be conducted without an IND if (1) it involves basic research not intended for immediate therapeutic, diagnostic, or similar purposes, or otherwise to determine the safety and efficacy of

[12] For information on determining whether human research with a radioactive drug can be conducted under a Radioactive Drug Research Committee (RDRC), see FDA's guidance for industry and researchers *The Radioactive Drug Research Committee: Human Research Without an Investigational New Drug Application* (the RDRC guidance).

the product, (2) the use in humans is approved by a Radioactive Drug Research Committee (RDRC) that is composed and approved by FDA, (3) the dose to be administered is known not to cause any clinically detectable pharmacological effect in humans, and (4) the total amount of radiation to be administered as part of the study is the smallest radiation dose practical to perform the study without jeopardizing the benefits of the study and is within specified limits.

B. 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. 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)):[13]

- 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.
- 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).

VI. SPECIFIC ISSUES CONCERNING THE APPLICATION OF THE IND REGULATIONS

[13] Note that studies using cold isotopes of approved drugs frequently 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 low doses and present low risk. In such cases, enforcement discretion would not be needed for these studies to be conducted without an IND.

This section addresses specific 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 under these circumstances. Therefore, these types of studies are clinical investigations and require an IND under part 312, unless the study meets the criteria for an exemption in § 312.2(b) or § 320.31(b) (see section IV) or the criteria in § 361.1, or the compound is labeled with a cold isotope and used in the manner described in section V, is a dietary supplement (see section VI.D.1), or is an article used for food or drink (i.e., primarily for taste, aroma, or nutritive value, rather than for some other effect on the structure or function of the body) in the study (see section VI.D.2).

B. Live Organisms

An IND is required for challenge studies in which a live organism (e.g., virus, bacteria, or fungi, whether 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 both 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 or the product meets the definition of a dietary supplement[14] or is an article used for food or drink (i.e., primarily for taste, aroma, or nutritive value, rather than for some other effect on the structure or function of the body) in the study. Similarly, an IND is required for a clinical investigation designed to evaluate whether colonization with a strain of bacteria can treat or prevent disease in patients with a chronic immune disorder.

C. Cosmetics

[14] Section 201(ff) of the FD&C Act does not specifically mention live organisms in the definition of a *dietary supplement* (21 U.S.C. 321(ff)), but does include more general language that results in some products containing live organisms falling within the dietary supplement definition, depending on the specific facts related to the product. The relevant language is found in section 201(ff)(1), which lists the substances that may be used as "dietary ingredients" in dietary supplements. Section 201(ff)(1)(E) provides that "dietary substance[s] for use by man to supplement the diet by increasing the total dietary intake" are dietary ingredients; section 201(ff)(1)(F) further defines *dietary ingredient* to include "a concentrate, metabolite, constituent, extract, or combination" of any other dietary ingredient. Taken together, these two provisions indicate that a live organism that is a constituent of an article that is commonly used as human food or drink (e.g., a probiotic in yogurt) may be used as a dietary ingredient in a dietary supplement.

Section 201(i) of the FD&C Act (21 U.S.C. 321(i)) defines a cosmetic as "(1) articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, and (2) articles intended for use as a component of any such articles; except that such term shall not include soap." With the exception of color additives and a few prohibited ingredients, a cosmetic manufacturer may use almost any raw material as a cosmetic ingredient and market the product without an approval from FDA.

As a general matter, studies of ingredients or products marketed as cosmetics require an IND if the ingredient is being studied for use to affect the structure or function of the body or to prevent, treat, mitigate, cure, or diagnose a disease (see 21 U.S.C. 321(g)(1); 21 CFR 312.2). This is true even if the study is intended to support a cosmetic claim about the ingredient or product's ability to cleanse, beautify, promote attractiveness, or alter the appearance, rather than a structure/function claim. For example, a study of the effect of a cosmetic product containing human or animal biological material (such as placenta) on skin repair mechanisms would require an IND, even if the study is intended only to support a claim of younger looking skin.

D. Foods

Those who are evaluating published clinical literature or sponsoring new clinical studies while conducting safety assessments for dietary ingredients, food additives (including food contact substances), and GRAS substances, as well as those who conduct or sponsor research intended to support labeling claims for conventional foods or dietary supplements, should be aware of two provisions of the FD&C Act that, depending on the circumstances, may restrict the marketing of products containing substances that have been the subject of "substantial clinical investigations" whose existence has been made public. Section 301(ll) of the FD&C Act (21 U.S.C. 331(ll)) prohibits the marketing of any food to which has been added a drug or biologic for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, unless the drug or biologic was marketed in food before any substantial clinical investigations involving the drug or biologic were instituted or one of the other exceptions in section 301(ll) applies. Section 201(ff)(3)(B)(ii) of the FD&C Act (21 U.S.C. 321(ff)(3)(B)(ii)) excludes from the dietary supplement definition any article authorized for investigation as a new drug for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, unless the article was marketed as a dietary supplement or as a conventional food before the IND became effective.[15] FDA interprets "authorized for investigation" to mean that the article is the subject of an IND that has gone into effect (see 21 CFR 312.40). Marketing the substance of interest "as a dietary supplement or as a food" (under section 201(ff)) or "in food" (under section 301(ll)) before seeking an IND or beginning any clinical investigations preserves the option to continue to market the substance in those forms after substantial clinical investigations have been instituted and their existence has been made public.

[15] FDA can create an exception to the exclusion by regulation, but only if the Agency finds that the use of the article in dietary supplements would be lawful. To date, no such regulations have been issued. The appropriate mechanism to request such a regulation is to file a citizen petition under 21 CFR 10.30.

1. Dietary Supplements

Under the Dietary Supplement Health and Education Act of 1994 (DSHEA), a *dietary supplement* is defined, in part, as a product taken by mouth that is intended to supplement the diet and that contains one or more dietary ingredients.[16] 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.

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,[17] 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., guarana and maximal oxygen uptake) 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 chronic diarrhea or constipation would need to be conducted under an IND.

2. Conventional Food

Section 201(f) of the FD&C Act (21 U.S.C. 321(f)) defines a *food* as "(1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article." For studies intended to evaluate the effects of a food, the analysis for whether an IND is needed turns on the intent of the clinical investigation.

As is the case for a dietary supplement, a food is considered to be a drug if it is "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease,"[18] except that a food may bear an authorized health claim about reducing the risk of a disease without becoming a drug (see section VI.D.3). Therefore, a clinical investigation intended to evaluate the effect of a food

[16] See section 201(ff) of the FD&C Act (21 U.S.C. 321(ff)).
[17] 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)(1)).
[18] 21 U.S.C. 321(g)(1)(B).

on a disease would require an IND under part 312. For example, a clinical investigation intended to evaluate the effect of a food on the signs and symptoms of Crohn's disease would require an IND.

The following paragraph in brackets [ ] is STAYED.

[The FD&C Act also defines *drug* to include "articles (other than food) intended to affect the structure or any function of the body."[19] This provision contains a parenthetical exception for foods that affect the structure and function of the body by virtue of providing nutrition to sustain life and health. Consistent with case law interpreting the "other than food" exception as applying to articles consumed primarily for taste, aroma, or nutritive value, FDA regulates conventional foods (including infant formula) that are intended to affect the structure or function of the body as foods, not drugs, as long as the intended structure or function effect derives from the product's character as a food — its taste, aroma, or nutritive value.[20] However, if an edible product that might otherwise be a conventional food is intended for a use other than providing taste, aroma, or nutritive value, such as blocking the absorption of carbohydrates in the gut, the product becomes a drug because the primary purpose of consuming it has changed. In other words, the product is no longer being consumed as a food — primarily for taste, aroma, or nutritive value — but used as a drug for some other physiological effect. Accordingly, a clinical investigation intended only to evaluate the nutritional effects of a food (including medical foods[21]) would not require an IND, but an investigation intended to evaluate other effects of a food on the structure or function of the body would. For example, a study of the effect of iron on hemoglobin levels in which subjects were fed beef or lamb as a source of iron would not require an IND, but a study of the effect of soy isoflavones on bone metabolism would. Similarly, a study of the ability of an infant formula to support growth of infants or of other nutritional properties of the formula would not require an IND. However, a study of other effects of the formula on the structure or function of the body (e.g., an investigation of the effects of docosahexaenoic acid in infant formula on visual acuity of infants) would require an IND.]

A clinical study intended to evaluate the safety of a food ingredient generally does not require an IND, even if the ingredient is known to have an effect on the structure and function of the body that is in addition to its taste, aroma, or nutritional effect. For example, a study of the safety of a flavor ingredient that has been found to bind to a receptor outside of the target location in the mouth would not require an IND if the intent of the study was to evaluate the safety of the ingredient when ingested as food. ***The following sentence in brackets [ ] is STAYED***. [In contrast, if the intent of the study was to evaluate the beneficial effects (beyond nutritional effects) of binding the newly found receptor, the study would require an IND.] Similarly, a clinical study may be performed to evaluate the tolerability of a food in a specific susceptible population, including individuals with a disease. In such an evaluation, biological parameters affected by the disease may need to be assessed in order to establish tolerance. For example, the

[19] 21 U.S.C. 321(g)(1)(C).

[20] See *Nutrilab v. Schweiker*, 713 F.2d 335 (7th Cir. 1983).

[21] A medical food is "a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation." 21 U.S.C. 360ee(b)(3).

administration of high intensity sweeteners to diabetic patients to establish no adverse effect on HbA1c levels or the administration of a novel food protein ingredient to a potentially allergic population to establish lack of allergic reactivity in this population would not require an IND. However, if the intent of the study was to demonstrate an effect of the food in decreasing HbA1c levels in diabetic patients or an effect of the food to desensitize or raise threshold levels of allergic reactivity in sensitive individuals, the study would require an IND.

Consistent with the considerations for conventional foods described in the previous paragraph, an investigation intended to evaluate the effects of a medical food on a disease would require an IND. However, if the medical food is simply being fed to subjects for nutritional purposes during a study examining the effects of another intervention, the use of the medical food in the study would not trigger the need for an IND, although the study might require an IND or investigational device exemption (IDE) for the intervention being studied.

3. Studies Intended to Support a Health Claim

NOTE: The stay does not apply to clinical investigations intended to evaluate whether a food substance may reduce the risk of a disease in individuals less than 12 months of age, those with altered immune systems, and those with serious or life-threatening medical conditions. This subsection is in effect for such clinical investigations.

The following paragraph in brackets [ ] is STAYED, except as noted above.
[Section 201(g) of the FD&C Act provides that a health claim in the label or labeling of a food (conventional food or dietary supplement) characterizing the relationship between a substance (food or food component) and a disease or health-related condition does not cause the food to be a drug on the basis of that claim, provided the claim is authorized under and made in accordance with the requirements of section 403(r)(1)(B) and (r)(3) of the FD&C Act[22] (for conventional foods) or under section 403(r)(1)(B) and (r)(5)(D) (for dietary supplements). Notwithstanding this provision, however, a clinical study designed to evaluate the relationship between a food substance and a disease and intended to provide support for such a claim is required to be conducted under an IND (21 CFR part 312), unless the substance-disease relationship being studied is already the subject of an authorized health claim. Section 201(g) provides, in effect, an exemption from the normal operation of the drug definition — it permits the use of health claims that would, without the exemption, cause a conventional food or dietary supplement to be a drug. However, the exemption does not apply until the health claim has been authorized by FDA. Therefore, a study conducted to support a new or expanded health claim would require an IND. For example, a study designed to evaluate whether vitamin D may reduce the risk of one or more site-specific cancers would require an IND, as there is currently no authorized health claim for this substance-disease relationship. Similarly, a study conducted to support a petition to amend the health claim for soluble fiber from certain foods and reduced risk of coronary heart disease (21 CFR 101.81) to include a new type of fiber would require an IND.]

E. Research With Noncommercial Intent

Some believe that the IND regulations do not apply to clinical investigations that are not intended to investigate a drug's potential for commercial sale. 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) or 320.31(b) (see section IV) or the criteria in § 361.1, 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 are a health care provider and 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 (see 21 CFR 312.2(b) and section IV.A of this guidance).

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 of 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 to determine whether the ingredient is lawfully marketed.[23] If the ingredient is not lawfully marketed, an IND is required 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), 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?

An IND generally would be required for a PET drug investigation, unless the investigation meets the criteria in 21 CFR 361.1. To meet these criteria, 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 an 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 an 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.[24]

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).

[23] Ordinarily, such inquiries would be directed to CDER, Office of Compliance, Office of Unapproved Drugs & Labeling Compliance.

[24] See the guidance for industry on *Botanical Drug Products*.

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 generally 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 11).

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 in place of the approved, finished product marketed by the 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.

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, in most cases, 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 FDA 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 telephone 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 telephone 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 (druginfo@fda.hhs.gov) or CBER's Division of Manufacturer's Assistance and Training (matt@cber.fda.gov), Office of Communication, Outreach and Development (both addresses and telephone 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 email, fax, or other written correspondence).

- They 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 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 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 archive formal inquiries and FDA responses to those 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.
- Guidance for industry on *CGMP for Phase 1 Investigational Drugs.*
- Guidance for industry and researchers on *The Radioactive Drug Research Committee: Human Research Without an Investigational New Drug Application*, which is intended to 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.
- Guidance for industry and FDA staff on *FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND: Frequently Asked Questions*, which is intended to clarify for sponsors how they can demonstrate compliance with the requirements of 21 CFR 312.120, as well as provide recommendations for the submission of information, whether in an IND or application for marketing approval for a drug or biological drug product, to demonstrate that a non-IND foreign clinical study was conducted in accordance with GCP.
- Guidance on *Emergency Use Authorization of Medical Products*, which is intended to inform industry, government agencies, and FDA staff of the Agency's general recommendations and procedures for issuance of Emergency Use Authorizations (EUAs).