Clinical studies involving probiotics
When FDA's investigational new drug rubric applies—and when it may not

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Researchers from a diverse array of scientific disciplines have focused and continue to focus on opportunities and areas for responsible clinical research involving the possible beneficial health effects of "probiotics." Investigators and researchers should be aware that not all clinical research involving probiotics reasonably falls within the requirements of the "investigational new drug" (IND) rubric administered and enforced by the US Food and Drug Administration. In determining whether an IND application is required before a clinical study may lawfully commence, investigators and researchers as well as institutional review boards should consider the regulatory classification, e.g., "drug," "new drug," "food," "food additive," "dietary supplement," etc. that applies to the substance under investigation. A potential probiotic product can fall along a continuum of regulatory classifications, each having implications on the nature and degree of regulatory requirements for clinical research and, ultimately, for claim substantiation and market access.

**Introduction**

The commensal microbiota is the subject of a diverse array of current and ongoing scientific study and investigation. Areas of study have involved disciplines ranging from microbiology, gastroenterology, and immunology to nutrition and food science. Modulating the microbiota has the potential to improve the health of the intestinal tract as well as improve the immune system and enhance the bioavailability of nutrients. Modulating the microbiota may also reduce the risk of certain diseases. Research involving each of the above-noted disciplines has focused on the possible role of "probiotics" in improving and enhancing the function of the microbiota.

Although "probiotics" have been variously defined, the most commonly cited definition is that advanced by the Food and Agriculture Organization of the World Health Organization, "live microorganisms which when administered in adequate amounts confer a health benefit on the host." The mechanisms by which probiotics may help achieve health benefits, in all likelihood, involve modifying the composition or function of gut microbiota, improving immune response, reducing colonic pH, bolstering intestinal barrier function, stimulating cell development, inhibiting gut pathogens and fostering nutrient absorption.

It follows that there is significant interest within various research communities with respect to investigating the therapeutic, nutritional, and functional effects of probiotics on the microbiota, and ultimately on human health. In this context, questions reasonably arise as to what US federal regulations and/or rubrics apply to the conduct of human clinical studies (hereinafter referred to as "clinical studies") focused on exploring and documenting the possible health-related benefits of probiotics. To this end, some confusion appears to exist on the part of researchers and institutional review boards (IRBs) with respect to whether clinical investigations of probiotics must be conducted in adherence to the Food and Drug Administration's ("FDA's") investigational...
new drug ("IND") requirements. This article is an effort to flesh out the general contours of the legal landscape that governs when clinical studies involving probiotics fall within the scope of the IND rubric—and, equally important, when they may not.

INDs in a Nutshell

Under the regulatory scheme in the United States, before clinical research can be performed with respect to the therapeutic/pharmaceutical-type benefit of a "new drug" or "biological product," the investigational new drug ("IND") provisions of the Food, Drug, and Cosmetic Act ("FD&C Act" or "the Act") come into play. Under these provisions, before such clinical trials can begin, the sponsor of the trial must notify FDA at least 30 days before the desired date for commencing the research. Extensive and detailed regulations govern the role and function FDA plays in evaluating and overseeing an investigational new drug ("IND") requirements. This article is an effort to flesh out the general contours of the legal landscape that governs when clinical studies involving probiotics fall within the scope of the IND rubric—and, equally important, when they may not.

Clinical Investigations Involving "Food" and "Dietary Supplements"

The IND rubric does not apply to all possible types of clinical research. In fact, as a general rule, the IND only rubric applies when the "intended use" of a product or substance serves to categorize the substance as a "new drug" or "biological product." "Intended use" is primarily determined by the sponsor's intent which can be manifested in product labeling and claims as well as in the terms and endpoints of the test protocol. It follows that clinical investigations of products or substances regulated as "foods" and "dietary supplements" are not subject to the rigors of the IND process unless the intended use or endpoint(s) investigated serve to also categorize the substance as a "drug" and "new drug" or "biological product." This critical distinction, however, has been blurred in the case of probiotics by virtue of an October 2010 FDA draft guidance titled "Investigational New Drug Applications (INDs)— Determining Whether Human Research Studies Can Be Conducted Without An IND."13

In the guidance, FDA broadly offered that an IND is required for studies "in which a live organism (e.g., virus, bacteria, or fungi that is modified or wild-type) is administered to subjects to study either the pathogenesis of disease or the host response to the organism." FDA went on to advise in the draft guidance that such a live organism would be considered a "biological product" and that an IND would be required for pursuing the clinical investigation of the substance. Probiotics are "live bacteria" and, thus, would appear to fall within this broad proscription regardless of their intended use.

Interpreted and followed literally, FDA's guidance would reflect the view that any clinical study involving a probiotic to be conducted under an IND regardless of the fact that the study is not designed to investigate any endpoint typical of a drug, data to take a number of years before completion and before an agency approval of the desired drug for a given indication is achieved (if ever).7

With the publication in February, 2012 of a final guidance "Early Clinical Trials with Live Bio-therapeutic Products: Chemistry, Manufacturing, and Control Information,"14 FDA appears to have taken steps to address this situation and avoid such broad interpretation. In this guidance, FDA makes clear that "the intended use of a product plays an essential role in how it is regulated" under the FD&C Act.15 And, to this end, "products that contain live microorganisms may be regulated as dietary supplements, foods, or drugs under the FD&C Act, depending on the product's intended use and other factors relevant to the statutory definition of the product category."16 Emphasis added. Thus, in its February 2012 guidance FDA appears to have made an effort to correct misunderstanding with respect to the applicability of IND requirements.17 This clarification squares well with and reinforces the comments in the agency's December 2006 draft guidance regarding complementary and alternative medicine products to the effect that "probiotics may be regulated as dietary supplements, foods or drugs...depending on ...intended use."18 Nonetheless, the fact that FDA has not revised its October 2010 IND guidance to conform with the above clarification (and, thus, reflect the fact that the IND requirements do not extend to all probiotic products) continues to serve as a basis for possibly confusing IRBs and, as result, discouraging investigators from pursuing
Regulatory Categories Applicable to Probiotic Research

As the above noted agency’s February 2012 and December 2006 guidelines underscore, the regulatory category or categories a given product or substance may fall within is generally determined by the “intended use” of the product or substance. With respect to probiotics and probiotic products, the categories include “food,” “dietary supplement,” and “drug” or “biological product.” The food and dietary supplement categories can be further broken down into “food additive”; “food” or “dietary supplement” bearing a “health claim”; “food” or “dietary supplement” bearing a “structure/function” claim, and “medical food.”

Drug, new drug and biological product. Determining drug and/or biological product status is fairly straightforward. An article is a “drug” if it is intended for the cure, mitigation, treatment, diagnosis, or prevention of disease. A drug is a “new drug” if it is not generally recognized by qualified experts as both safe (“GRAS”) and effective (“GRAE”) for its intended use. A new drug may not be lawfully marketed for any use until the use is the subject of an approved new drug application (“NDA”) or an approved supplemental NDA.

Determining whether a product is a “biological product” can be more complex. An article is a “biological product” if it contains a “virus, therapeutic serum, toxin, anti-toxin, vaccine, blood, blood component or derivative, allergenic product, or protein (except any chemically synthesized polypeptide) or analogous product applicable to the prevention, treatment, or cure of a disease condition.” FDA has broadly interpreted the term “analogous product” to include a variety of products that do not squarely fall within the other categories of the definition. Doing so permits the agency to keep up with advances in immunology, molecular biology, and other cutting edge disciplines. For example, the agency has interpreted the term “virus” to include “a product containing the minute living cause of an infectious disease and includes but is not limited to: bacteria.”

The definitions of drug, new drug, and biological product are not mutually exclusive. Accordingly, a product can be a drug, new drug and a biological product, depending on its composition and intended use(s). Moreover, a product or substance that, for example, meets the definition of “food” can also be a drug, new drug, or biological product depending on the intended conditions of use for which it is promoted or labeled or investigated. FDA applies the IND rubric to new drugs as well as biological products.

Dietary supplement. An article is a “dietary supplement” if, among other things, it is intended to “supplement the diet,” is or contains a “dietary ingredient,” is “intended for ingestion,” and is not in conventional food form. If a product meets the definition of a dietary supplement, no premarket approval system comparable to that of the NDA or biological license application (“BLA”) rubrics applies. Notification requirements apply, however, for “new dietary ingredients”—basically dietary ingredients not marketed in the United States prior to October 15, 1994. Nonetheless, this “notification” process does not require an FDA approval but merely requires that the company make the notification 75 days prior to marketing. Tellingly, a dietary supplement cannot be marketed for “drug-like” or disease prevention purposes.

Food. “Food” is defined in the FDC Act as an article “used for food or drink for man or other animals,” “chewing gum,” and articles used for “components of any such article.” Although foods per se are not subject to any premarket approval requirement, “food additives”—added to food that are not GRAS—are subject to premarket approval. Probiotic ingredients have for years been lawfully added to an array of foods, including, for example, milk and milk products as well as infant formula. Testing to support the safety and, thus, approval of a food additive has only infrequently involved human clinical testing and instead has almost exclusively been based on investigations with respect to laboratory animals. Human clinical studies of substances like probiotics, however, have recently become more frequent in light of the need to substantiate benefit claims advanced on behalf of such substances.

Medical food. A “medical food” is a special class of food that is defined as 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.” A medical food, thus, represents a unique regulatory category in light of the fact it is intended for use by a sick person and provides a distinct category in light of the fact it is intended for use by a sick person and provides a distinct disease condition and (2) helpful in the management of that condition. A medical food, thus, may be labeled and intended for the “management” of such a “disease condition” and avoid being classified as a drug, new drug or biological product within the meaning of the Act—and, thus, remain regulated as a “food.”

Foods and dietary supplements bearing “health claims.” With respect to claims made in the labeling of food and dietary supplements that expressly or impliedly characterize the relationship of a nutritive substance or food to a disease or health-related condition, FDA has special authority. This type of claim, is, in common parlance, referred to as a “health claim.” Before a health claim may be lawfully used on food, FDA must authorize the claim upon review of a petition for the claim and may only approve a claim upon finding that the claim is supported by “significant scientific agreement” among qualified experts.

Judicial rulings over the last decade have led to an additional category of health claims—“qualified health claims,” that also applies to foods and dietary...
supplements. In this case, FDA has implemented a policy of reviewing foods and supplementing even if the data and information in support of the claim may not meet FDA’s significant scientific agreement standard but the agency is nonetheless satisfied that "credible" information exists in support of the claim and that "qualifying" statements are consistent with the "reasonable" or "nonleading." As a general rule, health claims and qualified health claims are designed to inform healthy people of dietary practices that may help reduce the risk of contracting a disease condition.31

FDA-authorized model health claims and FDA-sanctioned model qualified health claims are cast in terms of the potential of healthful diets containing the food or substance at issue to "reduce the risk" of a given disease or condition.32

Thus, although a claim that healthful diets that include a given substance "may reduce the risk" of a given disease or health condition could be construed as a "prevention" claim that arguably would invoke the definitions of "drug," "new drug," and "biological product," FDA has explained the propriety of "may reduce the risk" health claims on foods by noting that the wording conveys:... to consumers that there is no guarantee that any one dietary practice will, in fact, reduce an individual’s risk of a disease... Absolute claims about diseases affected by diet generally are not possible because such diseases are almost always multifactorial, and that diet is only one factor that influence whether a person will get such a disease."33 Thus, a food bearing an authorized or sanctioned health claim involving risk reduction is not deemed to be a drug, new drug, or biological product.

Foods and dietary supplements bearing "structure or function" claims. Foods and dietary supplements may bear claims concerning the effect of the substance or product on the "structure or function" of the human body.34 The fact that foods and dietary supplements may bear structure/function claims on behalf of their products (assuming the claims can be substantiated as truthful and not misleading) reflects the fact that foods and supplements can clearly affect the structure or function of the human body and that a claim with respect to such an effect should not be regulated under the rigorous standards that govern drugs. FDA has, however, issued detailed regulations that differentiate between structure or function claims appropriate for dietary supplements (and by inference, appropriate for foods) and "drug" claims that may not be made on behalf of a "dietary supplement," or on behalf of a food without prior FDA authorization.35 For example, FDA has recognized that a claim that a probiotic food or supplement "helps maintain flora" is an appropriate structure/function claim36 because it does not imply an effect on disease and because it does not reference a drug, drug action, or therapy. That said, the agency has also opined that a claim that a probiotic product "helps individuals using antibiotics to maintain normal intestinal flora" is an implied drug claim to the effect that using such a product mitigates a disease condition.37

Considerations with Respect to When and Whether Clinical Research Involving Probiotics Is Subject to the Requirements of an IND

As discussed at the outset, because of the possible beneficial effects of probiotics, researchers from a diverse array of disciplines have focused and continue to focus on opportunities and areas for responsible clinical research involving probiotics. Clinical research, obviously, is essential to any effort to establish the safety of the use of new strains of probiotics in human populations and to clarify and precisely articulate the role of a given probiotic strain or strains in promoting human health. That said, investigators and researchers should be aware that not all clinical research involving probiotics reasonably falls within the requirements of an IND. Accordingly, before undertaking such research and in determining whether an IND is required before the study may lawfully commence, investigators and researchers as well as IRBs should take into consideration the "intended use" and, in particular, the intended focus and endpoint of a given study protocol.

As outlined above, FDA has broad authority under the FDC Act to classify and categorize products for human consumption based on their intended use. Different regulatory standards govern the marketing of a product depending on how the product is intended for use and, in turn, therefore classified under the FDC Act—a, i.e., as a “food,” a “food additive,” a “dietary supplement,” a “drug,” a “medical food,” etc. Stated otherwise, a potential probiotic product can fall along a continuum of regulatory classifications, each having implications on the nature and degree of conditions for clinical research and, ultimately, for claim substantiation and market access.

For a variety of reasons it appears that the dividing lines along the continuum have not always been carefully observed by researchers, IRBs, or even FDA. As a general rule, when a clinical investigation focuses on an endpoint involving the cure, mitigation, prevention, treatment, or diagnosis of disease, the IND rubric comes into play. On the other hand, if the focus of the study is solely (1) on the effect of a substance solely on the structure or function of the human body and no disease endpoint is implied or (2) on an endpoint falling within the scope of a "health claim" or "qualified health claim," a "medical food," etc. Stated otherwise, a potential probiotic product can fall along a continuum of regulatory classifications, each having implications on the nature and degree of conditions for clinical research and, ultimately, for claim substantiation and market access.

In sum, to avoid unnecessary (regardless of how well-intentioned) restraints on the contours of clinical research, researchers in crafting and IRBs in evaluating protocols should recognize that adherence to IND requirements generally should not be necessary when:

• Foods (including medical foods) or dietary supplements or the components of foods and dietary supplements are investigated to establish the safety of a given probiotic strain or strains for use in food or dietary ingredients;

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• Foods (including medical foods) or dietary supplements or the components of foods and dietary supplements are investigated to establish the safety of a given probiotic strain or strains for use in food or dietary ingredients;

• Foods or dietary supplements or the components of foods and dietary supplements are investigated for their effects on the structure or function of the human body (provided the effects under investigation do not fall within a clinical focus...
on the cure, mitigation, treatment, prevention, or diagnosis of disease; or

• Foods or dietary supplements or the components of foods and dietary supplements are investigated as part of a healthful diet to assess in healthy people a possible relationship between the food or supplement and the reduction of risk of a given disease or health-related condition (i.e., “health claims”); or

• Foods or food components are investigated for their ability to provide specific dietary management of a disease condition for which distinctive nutritional requirements apply (i.e., “medical foods”).

Clearly, real care needs to be taken in designing a clinical study and developing a protocol focused on ascertaining a possible health benefit of a food, medical food, or dietary supplement. Researchers and IRBs should routinely consult with counsel familiar with FDA laws and regulations to determine whether a substance is eligible to be investigated as a food, medical food, or dietary supplement and whether a desired protocol or course of study is conceived, structured and presented so as to entail food, medical food, and/or dietary supplement applications that fall well outside the intended use conditions that typify drugs, new drugs, and biological products and, thus, fall outside the requirements that a clinical study requires an IND. As need be, confirmation of appropriate food and/or dietary supplement status for the investigation should routinely be sought from FDA—for example, the agency’s Center for Food Safety and Applied Nutrition, Center for Drug Research and Evaluation, or Center for Biological Evaluation and Research.

None

This commentary is not intended to be or to substitute for legal advice.

16. 21 U.S.C. 321(g)(1)(B) (comprising “food” bearing a structure/function claim from part of the “drug” definition) and 343(b)(5)(C) (comprising a “dietary supplement” bearing a structure or function claim from the definition of “drug”).

21 C.F.R. 101.95.


34. In some cases, substances are excluded from the definitions of “food” and “dietary supplement,” respectively. Pursuant to 21 U.S.C. 333(b), it is unlawful to introduce into interstate commerce any food for which there has been added an approved new drug or a licensed biological product or a drug or biological product for which “substantial clinical investigations had been instituted and for which the investigational new drug has been found to be of public.” From the perspective of its framers, this prohibition makes sense—those intending to seek significant time and money to develop new drugs and biological products should not have to worry that others may take advantage of their research to market a new substance as a drug and thereby avoid any premarket approval requirements accompanying a new drug or biological product. The scope of the prohibition, however, is not clear and FDA has not issued definitive guidance on how it intends to interpret the provision. A broad interpretation could have the unintended consequence of significantly discouraging companies from sponsoring clinical research for food and dietary ingredients. Pursuant to 21 U.S.C. 333(b)(3), a dietary supplement cannot be an approved drug, certified antibiotic, and licensed biological product or new drug, antibiotic, or biological for which substantial clinical investigations has been instituted under INDs and for which the existence of such investigations has been made public. Moreover, when it is realized that this prohibition applies to even components of a dietary supplement as well as to the supplement itself. In rare cases, food ingredients or components, dietary supplements, and dietary supplement ingredients or components falling within the scope of either of these provisions cannot be accorded food or dietary supplement status and, as a result, cannot be investigated or subject to clinical study or if they were foods or dietary supplements. Thus, any clinical research of a substance excluded from the food or dietary supplement definition would, in all likelihood, fall within the IND rubric.
Letter to the Editor

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In my article “Clinical studies involving probiotics” appearing at pages 485–489 of the November/December 2012 edition of Gut Microbes, I address issues involving whether an investigational new drug application (“IND”) is required before a clinical study of a probiotic may lawfully commence. On page 488 I mention that researchers, when crafting protocols and IRBs when evaluating protocols, should recognize that adherence to IND requirements should not be necessary when, among other things, foods or dietary supplements or the components of foods and supplements are investigated to establish the “safety” of a given probiotic strain or strains for use in food or as dietary ingredients. Upon reflection, I fear there is a risk that this comment may be interpreted as suggesting that no regulatory considerations attend a decision to test the safety of a probiotic for food or dietary supplement use. Any such interpretation would not be correct. Issues with respect to the “safety” testing of a food or supplement ingredient merit an article of their own, but suffice to say for purposes of this note that a clinical study on a probiotic strain for any food or dietary supplement use should not commence unless strong scientific support for safety of the desired use already exists. Even when IRB authorization and informed consent are in hand, if it appears that the applicable statutory standards for establishing the safety of the intended use as a food or dietary supplement ingredient may not be met, sponsors and/or researchers, in my view, should, before commencing the desired study, contact FDA’s Center for Food Safety and Applied Nutrition and share with appropriate agency officials and solicit their reaction to the basis for any conclusion that such testing does not present a foreseeable risk to test subjects.

References