

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 bio-availability of nutrients. Modulating the

microbiota may also reduce the risk of certain diseases.¹

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.”² 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

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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.³

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”⁴ or “biological product,”⁵ the “investigational new drug” (“IND”)⁶ provisions of the Food, Drug, and Cosmetic Act (“FDC Act” or “the Act”) come into play.⁷ Under these provisions, before such clinical trials can begin, the sponsor of the trial must notify FDA at least 30 d before the desired date for commencing the research. Extensive and detailed regulations govern the role and function FDA plays in evaluating and overseeing an IND.⁸ Although FDA does not “approve” an IND, it nonetheless reviews and comments on the study protocols; considers information on the proposed drug’s chemistry, manufacturing, and controls; and carefully evaluates toxicology and pharmacology information from publicly available sources as well as pre-clinical studies. Moreover, FDA can request any additional information it deems necessary to ensure that it is reasonably safe to conduct a clinical trial. Needless to say, as a practical matter, a clinical trial should not begin under the IND process until FDA is satisfied with respect to the scope, design, and adequacy of the proposed trial. And, at any time during the conduct of the trial, FDA can place the study on “clinical hold” until any significant problem or concern is resolved to the agency’s satisfaction.

As a general rule, clinical investigations performed under an IND and conducted to support ultimate approval of a new drug involve a series of focused phases of study designed to provide critical information not only to ensure the safety and effectiveness of a given drug for a given indication but also to provide a basis to ensure that physicians and patients receive adequate directions for the safe and effective use of a given drug. It is common for this phased

regulatory scheme for the collection of 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).⁹

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 test 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”¹⁰ and “dietary supplements”¹¹ 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”¹² 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, new drug, or biological product, i.e., endpoints related to the cure, mitigation, treatment, prevention or diagnosis of disease. In light of the guidance, many IRBs may operate under the impression that they are required to request sponsors of probiotic clinical studies designed to investigate non drug-like or non-therapeutic endpoints to conduct such studies pursuant to an IND. Sponsors not contemplating true drug or biological product research and development may well balk at such a requirement. As a result, potentially valuable public health research is at risk of being inhibited or simply not pursued. And, in turn, the opportunity to communicate to consumers meaningful information related to the use of probiotic products may be lost.

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 FDC 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 misinforming IRBs and, as result, discouraging investigators from pursuing

probiotic clinical research **not** related to drug, new drug, or biological product endpoints. Stated otherwise, in spite of FDA's efforts to clarify the regulatory status of clinical investigations of probiotics, some researchers and IRBs are destined to remain uncertain as to when the agency's IND requirements apply. The following catalog of the regulatory categories applicable to probiotics is designed to provide the basis for researchers and IRBs to help assess when the IND route is required—and when it may not be.

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."¹⁹ 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."²⁰

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.²¹ 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.²² 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."²³ 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..."²⁴

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.²⁵ If a product meets the definition of a dietary supplement, no premarket approval system comparable to that of the NDA or biologics 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, 1994.²⁶ 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."²⁷ Although foods per se are not subject to any premarket approval requirement, "food additives"—added to food that are not GRAS²⁸—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 involving 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."²⁹ 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 nutritional requirement (1) necessitated by a patient's 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.³⁰ 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 and permitting health claims to appear on foods and supplements 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 can render the claim not misleading. 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 influences 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—i.e., as a "food," a "food additive," a "drug" or "new drug," a "dietary supplement," a "biological product," a food or dietary supplement bearing 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.

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 "medical food," the IND requirements should not, as a general rule,³⁸ come into play.

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;
- 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);

- 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”).

References and Notes

1. Collado MC. Role of Probiotics in Health and Diseases, HANDBOOK OF PROBIOTICS AND PREBIOTICS, Lee, K.L. and Salminen, S. eds, John Wiley and Sons (2d Ed. 2009).
2. Food and Agriculture Organization of the United States. 2001, Health and Nutritional Properties of Probiotics in Food Including Powdered Milk With Live Lactic Acid Bacteria. http://www.who.int/food-safety/publications/fs_management/en/probiotics.pdf.
3. This commentary does not address issues that may attend government-funded research.
4. “New drug” is a statutory term of art. See, *infra*, text accompanying footnotes 20 and 21 for discussion.
5. “Biological product” is also a statutory term of art. See, *infra*, text accompanying footnotes 22 and 23 for discussion.
6. 21 U.S.C. 355(i)
7. 21 U.S.C. 301, et seq.
8. 21 C.F.R. Part 312.
9. In addition to its IND regulations, FDA has issued comprehensive regulations governing the role of institutional review boards (“IRB”) with respect to reviewing clinical investigations within the IND rubric. 21 C.F.R. Part 56. The IRB regulations also apply to studies conducted within the investigation medical device rubric of the FDC Act as well as clinical investigations that support applications for research or marketing permits for products regulated by FDA including foods, dietary supplements, infant formulas, medical foods, and the like. Consistent with its IRB regulations, FDA also has issued extensive requirements with respect to ensuring that the rights and welfare of human subjects are protected and that subjects are fully informed about the risks, alternative treatments, and other relevant information before deciding to participate in any given clinical study. 21 C.F.R. Part 50. These “informed consent” requirements ensure that anyone undergoing a clinical study does so knowingly and voluntarily with a full understanding of the contours of investigation and secure in the knowledge that he or she may withdraw his or her consent at any time without penalty or recrimination.
10. Defined *infra* in text accompanying reference 27.
11. Defined *infra* in text accompanying reference 25.
12. Defined *infra* in text accompanying reference 21.
13. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM229175.pdf.
14. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/general/UCM292704.pdf.

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

15. *Id.*
16. *Id.*
17. Of course, any clinical study involving a substance meeting the definition of food or dietary supplement but focused on an endpoint involving the cure, mitigation, treatment or prevention of disease would not be exempt from the IND requirements.
18. “Draft Guidance for Industry: Complementary and Alternative Medicine Products and Their Regulation by the Food and Drug Administration,” December 2006; www.fda.gov/RegulatoryInformation/Guidances/ucm144657.htm.
19. Additional possible but less likely categories for probiotics include “medical device” and “cosmetic.”
20. And, the category can be broken down even further into animal food or feed.
21. 21 U.S.C. 321(g).
22. 21 U.S.C. 321(p).
23. 42 U.S.C. 262(i).
24. 21 C.F.R. 600.3(h)(1).
25. 21 U.S.C. 321(ff).
26. 21 U.S.C. 350b.
27. 21 U.S.C. 321(f).
28. 21 U.S.C. 321(s).
29. 21 U.S.C. 360ee(b)(3). FDA has, by regulation, expanded on the requirements for achieving “medical food” status, e.g., a medical food must be intended for the dietary management of a patient who, because of therapeutic or chronic medical needs, has limited or impaired capacity to ingest, digest, absorb, or metabolize ordinary foodstuffs or certain nutrients, or who has other special medically determined nutrient requirements, the dietary management of which cannot be achieved by the modification of the normal diet alone. 21 C.F.R. 101.9(j)(8).
30. 21 U.S.C. 343(r).
31. Nevertheless, FDA has observed that health conditions can be based on research involving subjects who have the disease or condition at issue: Health conditions involve reducing the risk of a disease in people who do not have the disease that is the subject of the claim. FDA considers evidence from studies with subjects who have the disease that is the subject of the claim only if it is scientifically appropriate to extrapolate to individuals who do not have the disease. That is, the available scientific evidence demonstrates that (1) the mechanism(s) for the mitigation of treatment effects measured in the disease populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations and (2) the substance effects these mechanisms in the same way in both diseased and healthy people.
32. See, e.g., 21 CFR 101.72 - 101.83.
33. 58 Fed. Reg. 1993; 2478:2505.

drugs, new drugs, and biological products and, thus, fall outside the requirement that a clinical study requires an IND. As need be, confirmation of appropriate food and/or dietary supplement status for the investigation of a given use of a probiotic can 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 Biologics Evaluation and Research.

Note

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

34. 21 U.S.C. 321(g)(1)(B) [exempting “food” bearing a structure/function claim from part of the “drug” definition] and 343(r)(6) [exempting a “dietary supplement” bearing a structure or function claim from the definition of “drug”].
35. 21 C.F.R. 101.93.
36. See 65 Fed. Reg. 2000; 1000:1029.
37. *Id.*
38. In some cases, substances are excluded from the definitions of “food” and “dietary supplement,” respectively. Pursuant to 21 U.S.C. 331(l), it is unlawful to introduce into interstate commerce any food to which 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 existence of such investigations has been made public.” From the perspective of its framers, this prohibition makes sense—firms intending to risk 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 test substance as a food and thereby avoid any premarket approval requirements accompanying a new drug or a 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. 321(ff)(3)(B), a dietary supplement cannot be an approved drug, certified antibiotic, and licensed biological product or new drug, antibiotic, or biological for which substantial clinical investigation has been instituted under INDs and for which the existence of such investigation has been made public. Judicial case law has established that this prohibition applies to even components of a dietary supplement as well as to a dietary supplement itself. In sum, 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 as 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.¹ 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

1. Degnan FH. Clinical studies involving probiotics: When FDA’s investigational new drug rubric applies and when it may not. *Gut Microbes* 2012; 3:485-9; <http://dx.doi.org/10.4161/gmic.22158>; PMID:23060015.

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