



International Scientific Association for Probiotics and Prebiotics

**Comment on
Docket No. FDA-2010-D-0503**

Submitted January 11, 2011 electronically to <http://www.regulations.gov>

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville MD 20852

Dear Sir:

The following comments are submitted by the International Scientific Association for Probiotics and Prebiotics (ISAPP) in response to the draft guidance, “Investigational New Drug Applications (INDs)—Determining Whether Human Research Studies Can Be Conducted Without an IND.”

ISAPP is an association of independent academic and industrial scientists involved in research on fundamental and applied aspects of probiotics and prebiotics. The scientists participating in ISAPP have a common interest in generating high quality scientific information for the probiotic and prebiotic fields and providing guidance for collaborative and multidisciplinary research. ISAPP is the only scientific organization dedicated specifically to probiotics and prebiotics, bringing together scientists from all pertinent disciplines, including food science, microbiology, immunology, biochemistry, nutrition, and medicine.

As scientists representing a broad variety of disciplines with an interest in probiotics and prebiotics for a range of applications—drugs, foods, and dietary supplements—we are greatly concerned about several aspects of the draft guidance proposed by the Centers for Drug Evaluation and Research (CDER) and Biologics Evaluation and Research (CBER). We applaud the effort to clarify the conditions under which filing of an investigational new drug application (IND) is mandated by law or regulation prior to initiation of human research, but we regard the draft guidance offered as seriously flawed. Our comments focus narrowly on probiotics and prebiotics, but some of the issues we address are broader.

1. Coverage and Authorship

While the draft guidance emphasizes human research studies of drugs and biologics, it also briefly addresses dietary supplements. Oddly, it never mentions food ingredients, although both probiotics and prebiotics (as well as other substances that may have effects on the structure or function of the body) have a long history of being regulated primarily as food ingredients. Both probiotics and prebiotics are widely used as ingredients in conventional foods and in such foods for special nutritional use as infant formula. Several prebiotic and probiotic ingredients have been approved and are currently used in infant formulas sold in the U.S. and internationally, and all of these ingredients were approved only after extensive human research. The point of this



discussion is that a long history exists of both the safety and the potential benefit on the structure or function of the body for substances intended for use in foods, and these benefits have been revealed in human research. Such research has *never* been conducted under INDs, *nor should it be* in that food applications—absent claims that the food or ingredient is useful in the diagnosis, cure, mitigation, treatment, or prevention of disease—are not drug uses.

The omission of discussion of human research on food ingredients is particularly problematic in that both FDA and the Federal Trade Commission (FTC) have explicitly required that such research be conducted to provide an adequate basis for health claims and, in many cases, for structure-function claims. Since both of these types of claims are authorized by statute, omission of consideration of human research to support them is unacceptable in a document that purports to provide useful guidance about when an IND is or is not necessary to conduct human research studies.

The draft guidance does, however, devote three paragraphs to dietary supplements. These paragraphs provide only the most cursory outline of the definition of a dietary supplement and the human research that may be performed with or without an IND. This lack of substantive discussion of food and dietary supplement ingredients suggests a lack of involvement or even consultation with staff of the Center for Food Safety and Applied Nutrition (CFSAN), where expertise in food and dietary supplement ingredients lies.

It is wholly inappropriate for CDER and CBER to offer guidance regarding human research on substances such as food or dietary supplement ingredients for which these two centers have no regulatory expertise or authority. ISAPP proposes that this deficiency can be rectified in one of two ways:

1. The focus of this guidance may remain on drugs and biologics under the authorship of CDER and CBER alone, but it must then include a specific acknowledgement that it does not address issues regarding human research into substances or live microorganisms intended for use as food or dietary supplement ingredients. If including this statement results in the guidance being unable to address some of the more contentious areas regarding INDs, this fact confirms ISAPP's opinion that authorship that fails to include CFSAN is inadequate.
2. Alternatively, this guidance can be expanded to substantively include human research for foods and dietary supplements with inclusion of CFSAN input to assure that human research targeted toward products regulated by CFSAN is adequately addressed, distinct from drug or biologic intended use; such a draft guidance incorporating CFSAN input and co-authorship would need to be expanded to more usefully address human research of food and dietary supplement ingredients. Subsequently, a second-round draft document can be issued.

2. Differentiating Between Drugs and Foods or Dietary Supplements

This discussion in the document is confusing and thoroughly inconsistent. While it is acknowledged (cursorily) that foods and dietary supplements, as well as drugs, can be intended



to affect the structure or function of the body, this fact is ignored in the draft guidance whenever it is inconvenient.

Lines 80-83: “It is important to note that the *drug* definition is not limited to compounds intended for a therapeutic purpose. 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.”

Lines 85-87: “Note, however, that 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.”

Lines 338-340: “...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.”

Lines 349-351: “Although the challenge organism [in research to study the host response to the organism] is not intended to have a therapeutic purpose, there is intent to affect the structure or function of the body. Thus, the organism is a biological product and a drug.”

Lines 371-373: “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.”

Three of the citations above claim that *any* intent to affect the structure or function of the body (or even an intent to discover if there is any such effect) triggers the requirement for an IND. The other two citations concede that such intent alone does not trigger such a requirement absent a therapeutic purpose.

In the opinion of ISAPP this draft guidance attempts to expand the definition of a drug to include all or nearly all effects on the structure or function of the body, ignoring the plain language of the law that the intention to have such effects may be commonly held for drugs and biologics, foods and food ingredients, and dietary supplements and dietary ingredients. Indeed, the statements on lines 338-340 and 349-351, quoted above, explicitly and incorrectly claim that the mere fact of intention to affect the structure or function of the body transforms any product into a drug.

Once again, the root cause of this serious deficiency is the willful disregard by the authors of this document of the lawful use of foods and dietary supplements to impact the structure and function of the human body and reduce the risk of disease, thereby imposing unreasonable bureaucratic hurdles to much needed research. *Not all human studies are drug studies*; neither CBER nor CDER has the authority to control studies designed to understand the role of foods in human health.



3. Human Studies with Structure or Function Endpoints

This concern is closely related to that expressed in the previous discussion. CDER and CBER are taking the position that some studies with endpoints related only to normal structure and function require INDs and others do not. If the guidance is to be useful, it must have a comprehensive discussion of why this is the case, with clear and unambiguous differentiation between the conditions that place a given human study into the IND-yes or IND-no box. This differentiation must be illustrated with informative examples of both types. ISAPP believes that this can only be done with the participation of CFSAN.

4. The Role of Current Health Status

In lines 519-520, responding to the question of whether human studies that enroll only healthy individuals may be required to be conducted under INDs, the draft guidance states, “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.” While ISAPP certainly agrees that many studies using only healthy individuals may require IND’s, the quoted statement conflicts with oral guidance that many of us have received. That is, we have previously been told that the clinical condition of study subjects *does* make a difference—that any human study enrolling patients with a disease or disorder requires an IND, even if the study endpoint does not address any potential treatment or amelioration of the underlying disease. ISAPP would appreciate clarification of this point—e.g., examples could be provided of human research in which food or dietary supplement ingredients are studied in patients and for which INDs would not be required.

5. Human Research on foods, dietary supplements and medical foods

As already indicated, foods are lawfully the subject of human research. In addition to structure or function endpoints, foods can be used for the reduction of the risk of disease (allowable on health claims) and medical foods can be used for the specific dietary management of a disease or condition. As these are appropriate uses for foods, research designed to establish the role of foods in these functions cannot legally be required to be conducted under an IND. The guidance document as written does not provide for clear paths for such research to be conducted without an IND and is to that extent deceptive.

Additionally, research endpoints do not necessarily equal intent for marketing purposes. A substance is a drug (and therefore would require to be researched under an IND) based on intent of use, not on endpoints selected in human studies. ISAPP requests the agency to recognize that research endpoints are not product labels, and research targeted to better understand mechanisms of action and biological activity of a food must be allowed to proceed without the requirement of an IND.

Further, the guidance document should specifically discuss the fact that a single substance or a single microorganism may simultaneously have food, dietary supplement, and drug applications, with the assignment based only on intent. (Perhaps the best known example is



niacin.) While recent statutes have barred the use of drugs—i.e., substances or microorganisms originally intended for use as drugs or biologics—from becoming ingredients in foods or dietary supplements, Congress did not intend to prevent the conduct of needed research—including human research—on ingredients intended for use in food or dietary supplements that were not previously developed and researched as drugs. It is important to note that many microorganisms have a long history of use in food production and in fermented foods, and human research using these microorganisms—absent an *intent* to market them for the cure, mitigation, treatment, or prevention of disease—is not drug research and does not require an IND.

In summary, the current draft guidance, in the opinion of ISAPP, does not provide information that would help a researcher studying a probiotic or a prebiotic understand when an IND is or is not required. It seems likely that the draft guidance as it currently exists *would tend to indicate that all human research must be performed under an IND*. Indeed, the current draft appears intended to tilt the playing field in the direction of giving control of human research on probiotics and prebiotics to CBER rather than CFSAN, a situation that ultimately would preclude the lawful investigation of and eventual use of probiotics as foods or dietary supplements.

Respectfully submitted by:

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