International Scientific Association for Probiotics and Prebiotics

To advance scientific excellence in probiotics and prebiotics

June 28, 2016

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Filed electronically at *https://www.regulations.gov/document?D=FDA-2010-D-0503-0076*

RE: Docket No. FDA-2010-D-0503-0075 (Oct. 30, 2015); Docket ID: FDA-2010-D-0503; Investigational New Drug Applications—Determining Whether Human Research Studies Can Be Conducted Without an Investigational New Drug Application; Guidance for Clinical Investigators, Sponsors, and Institutional Review Boards; Partial Stay and Republication of Guidance. (Herein referred to as the "Stay")

Dear Sir or Madam:

We would like to comment on the Federal Register notice issued by the Food and Drug Administration announcing a partial stay of portions of FDA's final Guidance for clinical investigators, sponsors, and institutional review boards titled "Investigational New Drug Applications—Determining Whether Human Research Studies Can Be Conducted Without an IND" (Oct. 30, 2015) (Herein referred to as the "Guidance").

While we are pleased that such a move by the Agency reflects its acknowledgment that the final Guidance is in error, we consider this Stay to be an inadequate response. We remain concerned that the Guidance, even with certain provisions stayed, will hinder the progress of legitimate and needed human research on foods and dietary supplements. Universities or the NIH may remain concerned about FDA's intent under the Guidance in its current form and may insist that researchers obtain an IND even when the research proposed is legally permissible under the Food Drug and Cosmetic Act. We are especially concerned that the FDA may continue to require IND's for research on foods or dietary supplements when the research is to be conducted on infants, the elderly, people under stress or on reduction of disease endpoints.

We expand on our concerns here:

FDA's mission and authority

The FDA has as its mission to protect and promote the health of Americans. Foremost in this context is the protection of study subjects. The FDA seems to be using the IND rubric as a means to oversee research to be certain it is safe. This is not the purpose of the IND. The IND was designed for companies interested in marketing a drug to be sure all characteristics of a drug were met along the research

pathway. The tool is wholly unsuited for managing research that is NOT intended to lead to a drug. The FDA should develop a process whereby, in working with IRBs, issues such as product identity and potential risks to subjects are determined and then an informed, reasonable decision about whether or not research should proceed can be made. INDs should be used ONLY for the development of new drugs, not for trying to control research. There are much better ways to safeguard study subject safety.

Further, the Stay does not address a fundamental flaw in the final IND Guidance, in which FDA asserts that it will apply IND requirements to clinical studies based on the biological endpoint to be explored as part of that study. Even with the Stay, the FDA imposes IND requirements under Part 312 to articles that do not constitute "new drugs" and thus have never been subject to such requirements. The Agency fails to address key stakeholder comments, which explain that longstanding case law holds that it is the objective intent of the vendor of an article of food, dietary supplement, or cosmetic that determines whether the article constitutes a "drug" and may be subject to IND requirements. The Agency again provides no support for the notion that a person who contributes to research of an article's biological endpoints can somehow determine objective intent with respect to the uses of that article for the purposes of classification under the FDCA.

The Agency provides no explanation for its authority to apply IND requirements based on the design of a clinical study. Even under the partial Stay, the Final IND Guidance continues to exceed FDA's authority under the Federal Food, Drug & Cosmetic Act. We reiterate that the FDCA clearly statutory framework underlying Part 312, which invokes FDCA section 505(i) and thus expressly limits FDA's authority to require INDs to articles that constitute "new drugs" as a matter of law

The partial Stay does not impact the section on 'Live Organisms', which has a negative impact on probiotic research.

The Guidance stipulates that the FDA would expect an IND for research involving live organisms, including wild-type bacteria or fungi. Specifically noted in the section is research focused on 'host response' to the organism, not intended to have a therapeutic purpose but to affect the structure and function of the body. The Guidance notes the exemption for dietary supplements or foods. But in the case of an investigational product that is not yet marketed as a food or dietary supplement, researchers would benefit from a clear statement by the FDA that research on live microorganisms (or probiotics) focused on host response to the organism and impacting the structure and function of the body does not require an IND.

The lack of clarity of the Guidance in this regard is apparent when considering examples of studies that would be reasonable for a probiotic. It is not clear, with the Stay in place, if the FDA would require an IND or not for the following non-exhaustive list:

1. Study of probiotic yogurt (food) on healthy children taking an antibiotic, with the endpoint being reducing the risk of antibiotic-associated GI side effects due to a disturbed gut microbiota.
2. Study of probiotic yogurt (food) on healthy children taking an antibiotic, with the endpoint being improved compliance of taking antibiotic.
3. Study of probiotic yogurt (food) on healthy adults, with the endpoint being symptoms of lactose intolerance.
4. Study of a probiotic dietary supplement on immune system endpoints such as cytokines, macrophage activation, salivary immunoglobulins in healthy adults and kids.
5. Study of a probiotic medical food for diabetics to determine on insulin usage in diabetic patients.

6. Study of a probiotic medical food to determine its effect on satiety and calorie intake in free living obese adults
7. Study of a probiotic food on free living adults with mild to moderate IBS to determine impact on GI symptoms, including gas, bloating, abdominal pain.
8. Study of a probiotic supplement on healthy children on incidence of common infectious diseases.
9. Study of a probiotic foods on inpatients (not critically ill) to determine effect on reducing nosocomial infections.
10. Study of a probiotic dietary supplement on inflammation associated with obesity.
11. Study of a probiotic dietary supplement on inflammation associated with diabetes.

The partial Stay does not lift the IND requirement for research in individuals less than 12 months of age or those with altered immune systems.

Although we recognize the added safety concerns involved with studies of infants or those with compromised immune systems, we reiterate that research on foods targeted toward these groups of people should proceed based on the demonstration of safety of the proposed research. The IND process is not appropriate for food research. Further, it is not clear how the FDA defines people with altered immune systems. An altered immune system could apply to otherwise healthy people who might be pregnant, elderly or under stress. Research on foods or dietary supplements in those populations should clearly be allowed to proceed without an IND as long as the proposed research is safe.

FDA should withdraw, rather than Stay, the Final IND Guidance.

We are concerned with the decision to issue a Stay in response to the outcry on the Guidance because a Stay can be lifted quite easily. This is a temporary solution to a very large problem for conducting human research on foods in the United States. The FDA should signify to all concerned stakeholders that it recognizes the error in the Guidance and respond by withdrawing it. Only then can all stakeholders be clear about FDA intent.

Conclusions

For these reasons, we urge the Agency in the strongest possible terms to promptly withdraw the Final IND Guidance and issue a notice to clinical investigators, sponsors, and Institutional Review Boards that the policy stated in sections VI.C and VI.D of the Final IND Guidance will not be enforced by the Agency and should not be enforced by Institutional Review Boards or other persons.

Instead of this flawed Guidance, the FDA should develop an approach for the need for INDs based on vendor's intent and safety of the proposed research.

Thank you in advance for your consideration of these comments.

Sincerely,

The Board of Directors, ISAPP:

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