FDA Partially Stays Controversial Policy of Requiring INDs for Clinical Studies Evaluating Food, Dietary Supplements and Cosmetics

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On Friday, October 30, 2015, FDA issued a Federal Register notice announcing a partial stay of the agency's controversial Final IND Guidance entitled, "Investigational New Drug Applications—Determining Whether Human Research Studies Can Be Conducted Without an IND" ("the Final IND Guidance"). FDA's administrative stay was issued in response to public comments from the academic community, trade associations, and other stakeholders that questioned the legal basis for the FDA policy articulated in the Final IND Guidance to require INDs for clinical research studies designed to evaluate certain types of biological effects of conventional food, dietary supplement, and cosmetic products. Public comments from key trade associations objected to FDA's classification of conventional foods, dietary supplements and cosmetics as "new drugs" for IND regulatory purposes based on the questionable "intent to study" criterion, rather than the vendor's intent that the article be used for conventional food, dietary supplement, or cosmetic purposes.

While FDA's partial stay of the 2013 Final IND Guidance provides some reprieve from IND enforcement for certain clinical research studies designed to evaluate conventional foods and dietary supplements, the stay does not reach studies evaluating cosmetics. The stay also does not address the legal rationale FDA offered in the Final IND Guidance to justify its policy to require INDs for studies evaluating conventional food, dietary supplements, and cosmetics. FDA continues to maintain its authority to require INDs for clinical studies of articles that do not constitute "new drugs" as a matter of law.

Under the partial stay, FDA will not enforce some of the more controversial IND requirements for conventional food and dietary supplement studies that are stated in the Final IND Guidance, at least for now. The stay stops short of the withdrawal of the guidance that was requested in public comments filed by key stakeholders.

Background

In October 2010, FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) jointly issued a draft form of the guidance ("the Draft Guidance") that was characterized as "clinical/medical." The Draft Guidance contained no mention of foods or cosmetics and included only a brief section on dietary supplements. In September 2013, FDA issued

the Final IND Guidance in an expanded form which included highly controversial provisions in newly added sections VI.C and VI.D. In these new sections of the guidance, FDA asserts that INDs must be filed before clinical research studies can be done which evaluate certain types of biological effects of conventional foods, dietary supplements, or cosmetics. More specifically, under the Final IND Guidance, FDA asserts that INDS are required for the following types of clinical studies.

- Clinical Studies Designed to Evaluate Non-Nutritional Structure-Function Effects of Conventional Foods **[STAYED].**
    - *"[A] clinical investigation intended only to evaluate the nutrition effects of a food (including medical foods) would not require and 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 would not require an IND if the intent of the study was to evaluate the safety of the ingredient when ingested as food. 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."*
- Clinical Studies Designed to Evaluate Disease Related Effects of Dietary Supplement or Conventional Food.
    - *"[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."*
    - *"[A] clinical investigation intended to evaluate the effect of a food on a disease would require an IND . . . 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."*
- Clinical Studies Designed to Support a Health Claim for a Dietary Supplement or Conventional Food **[STAYED IN PART].**
    - *"[A] clinical study designed to evaluate the relationship between a food substance and a disease and intended to provide support for . . . a [health claim] is required to be conducted under an IND . . ., unless the substance-disease relationship being studied is already the subject of an authorized health claim. . . . [F]or 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."*

- Clinical Studies Designed to Evaluate Structure-Function or Disease Related Effects of Live Organisms.
    - *"An IND is required for challenge studies in which a live organism . . . is administered to subjects to study the pathogenesis of disease or the host response to the organism . . . 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 . . . and a drug, and an IND is require for the clinical investigation, unless the criteria for [IND exemption] . . . are met or the product meets the definition of a dietary supplement 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."*
- Clinical Studies Designed to Evaluate Structure-Function or Disease Related Effects of Cosmetics.
    - *"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 . . . . 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."*

In all cases, the Final IND Guidance specifies IND requirements for studies involving conventional foods, dietary supplements, and cosmetics based on the design of the clinical study to evaluate certain types of physiological endpoints. The agency takes the controversial position that the intent to study certain physiological effects of a conventional food, dietary supplement, or cosmetic renders the article a drug in the context of a clinical research study, and in turn triggers IND requirements for the study.

After interested parties objected to the unexpected addition of sections IV.C and VI.D in the 2013 Final IND Guidance, FDA invited public comment on the Final IND Guidance in February 2014. In announcing the stay of certain parts of these sections of the Final IND Guidance, FDA noted that it "received comments from trade organizations, individual companies, scientific associations, public interest organizations and individuals" and that those comments "raised questions about application of the IND requirement to certain clinical studies of conventional foods, dietary supplements, and cosmetics being investigated for uses covered by the drug definition" of the Federal Food, Drug & Cosmetic Act.

FDA's Partial Administrative Stay

Under the recently announced administrative stay, FDA is staying the portions of subsection VI.D.2, in which the agency has taken the position that IND requirements apply to clinical studies designed to evaluate non-nutritional structure-function effects of conventional food. In addition, the agency is

staying all of subsection VI.D.3, in which the agency has taken the position that INDs are required for clinical studies designed to support health claims for conventional foods or dietary supplement, but has excluded from the stay clinical studies evaluating whether a food substance reduces the risk of a disease in individuals less than 12 months old (infants), those with altered immune systems, and those with serious or life-threatening medical conditions.

See Appendix A for a summary of the IND requirements FDA intends to enforce with respect to clinical research studies evaluating the effects of conventional food, dietary supplements and cosmetic products under the partial administrative stay.

Analysis

Under the partial administrative stay, FDA intends to refrain from enforcing some of the more controversial provisions of the 2013 Final IND Guidance that apply to conventional foods and dietary supplements. At least for now, the stay offers some relief from the burdensome IND requirements for conventional foods and dietary supplements, but the stay does not resolve the issues presented by the IND guidance that have given rise to the controversy. Notably, FDA's notice concerning the administrative stay provides little information concerning the agency's rationale in issuing the partial stay and does not respond to public comments specifically or explain why the agency has declined to withdraw the guidance, as requested by key stakeholders. Notably, the stay does not extend to provisions of the 2013 Final IND Guidance in which FDA states its questionable legal rationale for imposing IND requirements on clinical studies involving conventional food, dietary supplement, and cosmetic products. As a result, these provisions still stand. FDA is maintaining the position that the agency can impose IND requirements for clinical research studies based on the design of a clinical study to evaluate particular types of biological endpoints, rather than the vendor's intent with respect to the uses for which the conventional food, dietary supplement, or cosmetic would actually be marketed.

The agency does not account for the statutory framework that led to the promulgation of IND requirements, which clearly limits imposition of IND requirements to articles that constitute "new drugs" as a matter of law. The agency does not offer any support for the notion that the intent of a clinical study can unilaterally alter the intended use of an article and render a food or dietary supplement a "new drug" under the FDCA. As such, even with certain portions stayed, the 2013 Final IND Guidance continues to present significant substantive issues related to FDA's authority to implement IND requirements as intended.

From a procedural standpoint, it is both unprecedented and peculiar that FDA would choose to stay the selected portions of the Final IND Guidance rather than withdraw it and reissue the guidance without those portions. We have not identified any other instance of FDA administratively staying a guidance or a portion of a guidance. Indeed, regulations establishing the Agency's "Good Guidance Practices" make no reference to the capacity to administratively stay a guidance and explain that "FDA will periodically review existing guidance documents to determine whether they need to be changed or withdrawn."

Language used in the preamble suggests that FDA may view the stay as a partial, temporary resolution while it gathers more information. However, even with certain portions stayed, the Final IND Guidance continues to suggest that FDA can impose IND requirements based on the intent of a clinical study, rather than the intended use of the article used in the study.

Conclusion

The Federal Register notice does not provide a deadline for the submission of comments. In addition to the standard mechanism for submitting written comments, the notice takes the unusual step of explaining the process for submission of comments with confidential information that a party does not wish to be made publicly available.

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Appendix A – Breakdown of Specified Instances when IND Not Required and Required under Partial Stay of Guidance

Article	**IND Not Required**	**IND Required**
Food	Clinical studies designed to evaluate whether a conventional food may reduce the risk of a disease, intended to support a new or expanded health claim, and conducted in a population that does not include individuals less than 12 months old, those with altered immune systems, or those with serious or life-threatening medical conditions	Clinical studies designed to evaluate a conventional food's ability to diagnose, cure, mitigate, treat, or prevent a disease, except for studies designed to evaluate whether a conventional food reduces the risk of a disease, intended to support a health claim, and conducted in a population that does not include individuals less than 12 months old, those with altered immune systems, or those with serious or life-threatening medical conditions. Clinical studies designed to evaluate whether a food substance reduces the risk of a disease, intended to support a new or expanded health claim, and conducted in a population that includes individuals less than 12 months old, those with altered immune systems, or those with serious or life-threatening medical

		conditions.
Dietary Supplement	Clinical studies designed to evaluate whether a dietary supplement may reduce the risk of a disease, intended to support a new or expanded health claim, and conducted in a population that does not include individuals less than 12 months old, those with altered immune systems, or those with serious or life-threatening medical conditions.	Clinical studies designed to evaluate a dietary supplement's ability to diagnose, cure, mitigate, treat, or prevent a disease, except for studies designed to evaluate whether a dietary supplement reduces the risk of a disease, intended to support a health claim, and conducted in a population that does not include individuals less than 12 months old, those with altered immune systems, or those with serious or life-threatening medical conditions. Clinical studies designed to evaluate whether a dietary supplement reduces the risk of a disease, intended to support a new or expanded health claim, and conducted in a population that includes individuals less than 12 months old, those with altered immune systems, or those with serious or life-threatening medical conditions.
Cosmetics	Not specified	Clinical studies designed to evaluate a cosmetic's effect on the structure or function of the body or its ability to diagnose, cure, mitigate, treat, or prevent a disease.