Docket No. FDA-2010-D-0503

COMMENTS

of

THE WASHINGTON LEGAL FOUNDATION

to the

FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH & HUMAN SERVICES

Concerning

GUIDANCE FOR CLINICAL INVESTIGATORS, SPONSORS, AND INSTITUTIONAL REVIEW BOARDS ON INVESTIGATIONAL NEW DRUG APPLICATIONS — DETERMINING WHETHER HUMAN RESEARCH STUDIES CAN BE CONDUCTED WITHOUT AN INVESTIGATIONAL NEW DRUG (IND) APPLICATION

IN RESPONSE TO THE PUBLIC NOTICE PUBLISHED
AT 78 *FED. REG.* 55262 (SEPTEMBER 10, 2013)

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April 8, 2014

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Re: Guidance for Clinical Investigators, Sponsors, and Institutional Review Boards on Investigational New Drug Applications—Determining Whether Human Research Studies Can Be Conducted Without an Investigational New Drug (IND) Application
78 Fed. Reg. 55262 (September 10, 2013)
Docket No. FDA-2010-D-0503

Dear Sir/Madam:

The Washington Legal Foundation (WLF) appreciates this opportunity to submit comments in response to the Food and Drug Administration's (FDA) Guidance (cited above) regarding human research studies.

WLF shares the concern, expressed by numerous individuals and organizations in their comments, that the Guidance could have a paralyzing effect on clinical research in the U.S. and stifle innovation and product development. WLF is particularly concerned by the expansion of IND requirements to cover conventional food and medical foods, areas that have not previously been thought to be covered by those requirements. WLF writes separately to focus on FDA's statutory authority and to explain why FDA lacks authority to apply IND requirements to foods.

The Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to except certain "investigational" drugs from statutory provisions prohibiting the distribution and sale of new drugs that lack FDA marketing approval. 21 U.S.C. § 355i. The statutory exception is limited to

"drugs intended solely for investigational use." *Id.* It authorizes FDA, as a condition for granting an exception, to require the sponsor of the clinical investigation to submit an investigational new drug application (IND) that provides detailed information about the investigation. § 355i(1) & (2). Thus, FDA's authority to require INDs is limited to investigation of substances that qualify as "drugs"—indeed, is limited to only a subset of drugs that are intended for "investigational use."

Food, whether conventional or medical, as customarily marketed does not meet the FDCA's definition of a "drug." The term "drug" means, *inter alia*, "articles (other than food) intended to affect the structure of any function of the body of man or other animals." 21 U.S.C. § 321(g)(1)(C). In other words, food is not a "drug" so long as it qualifies as "food." The Guidance fails to provide any coherent explanation regarding why conventional food and medical food, as customarily marketed, should not be classified as "food." As such, they are not "drugs," and thus FDA lacks statutory authority to subject them to IND requirements.

Indeed, FDA regulations have long understood that the agency's IND requirements apply only to investigational drugs. The Guidance seeks to change that understanding, by applying the IND requirements to food that is already being sold to the public (and thus cannot plausibly be deemed "investigational") simply because someone plans to undertake a clinical study of the food's physiological effects on the human body. Moreover, the food is to be deemed a "drug" only for purposes of the clinical study, and that designation will end the moment the study is completed. Even if this new understanding were a plausible interpretation of FDA's statutory mandate (which it is not), FDA may not revise its previous regulatory interpretation of its

statutory mandate by means of a guidance document. Rather, the Administrative Procedure Act requires FDA to undertake any such revisions by means of formal notice-and-comment rulemaking. Accordingly, FDA should withdraw Sections VI(D)(2) & (3) of the Guidance, which seek to impose IND requirements on conventional food and medical food.

I. *Interests of WLF*

The Washington Legal Foundation is a public interest law firm and policy center with members and supporters in all 50 States. WLF regularly appears before federal and state courts and administrative agencies to promote economic liberty, free enterprise, a limited and accountable government, and the proper conduct of our state and federal administrative systems. To that end, WLF has frequently appeared in judicial and administrative proceedings to ensure that administrative agencies adhere to the rule of law. *See, e.g., Shinseki v. Sanders*, 556 U.S. 396 (2009).

In particular, WLF focuses much of its work on the activities of the Food and Drug Administration. WLF has repeatedly criticized FDA for failing to comply with the Administrative Procedure Act (APA) when adopting new rules intended to have broad application. For example, litigation filed by WLF on behalf of patients and doctors forced FDA in 1994 to retract rules regarding the regulation of allograft heart valves, after FDA conceded that it had not complied with the APA's notice-and-comment procedures before adopting the rules. *Washington Legal Found. v. Shalala*, No. 93-5279 (D.C. Cir. 1994). In a recent case in which WLF played an active role, a federal district court overturned an FDA product classification decision, in substantial part because FDA failed to abide by the APA before

changing a long-time regulatory interpretation. *Prevor v. FDA*, 895 F. Supp. 2d 90 (D.D.C. 2012). Since 2006, WLF has operated its "OPDP Watch" project, which critiques warning letters and "untitled" letters issued by FDA's Office of Prescription Drug Promotion (formerly known as DDMAC). A recurring theme of WLF's critiques is that OPDP regularly announces new legislative rules by means of its warning letters, yet does so without abiding by the APA's notice-and-comment procedures.

II. *Statutory Background*

Congress adopted the Federal Food, Drug, and Cosmetic Act (the "FDCA"), 21 U.S.C. §§ 301 *et seq*., to regulate the sale and distribution of drugs to the public. The FDCA bars the introduction of any "new drug" into interstate commerce unless FDA has approved a marketing application from the drug's sponsor. 21 U.S.C. § 355(a). FDA does not even consider granting such applications until after the sponsor has provided substantial evidence that the drug is safe and effective for its intended use. 21 U.S.C. § 355(b) & (j). Sponsors cannot, of course, gather evidence of safety and effectiveness unless they are permitted to conduct human research studies of the as-yet-unapproved new drug. Accordingly, FDA is authorized by the FDCA to grant exceptions to § 355(a) in order to permit studies of "drugs intended for investigational use," thereby allowing sponsors to gather the data necessary to support a new drug application (NDA). 21 U.S.C. § 355i. The Act further authorizes FDA, as a condition for granting an exception, to require the sponsor of the clinical investigation to submit an IND that provides detailed information about the investigation. § 355i(1) & (2). Thus, FDA's authority to require INDs is limited to investigation of substances that qualify as "drugs"—indeed, is limited to only a subset

of drugs that are intended for "investigational use." FDA's Part 312 regulations, which govern INDs, state that an IND can be required for a clinical investigation only if the research involves a "drug" as that term is defined in FDCA. The Guidance explicitly acknowledges this "drug" requirement. Guidance at 2-3.

Thus, whether FDA possesses statutory authority to impose IND requirements on clinical investigations of food turns largely on whether the conventional food or medical food is a "drug." The FDCA defines the term "drug" as follows:

> The term "drug" means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animal.

21 U.S.C. § 321(g)(1).

WLF recognizes that the terms "food" and "drug" are not mutually exclusive. Thus, under § 321(g)(1)(B), if a manufacturer distributes a food with the intent that it be used "in the diagnosis, cure, mitigation, treatment, or prevention of disease in man," the food is also a drug. Moreover, if the manufacturer undertakes a clinical study of a food for the purpose of supporting a subsequent NDA that would allow the marketing of the food for such use, the IND requirements undoubtedly apply to the study.

For purposes of the Guidance, however, the key provision of the "drug" definition is Part (C), which covers articles "intended to affect the structure or any function of the body of man or other animal." That part explicitly exempts "food" from inclusion within the definition. The

FDCA also provides that a health claim in the label or labeling of a food characterizing the relationship between a food and a disease or health-related conditions does not cause the food to be a drug on the basis of that claim, provided that certain conditions are met. *See* 21 U.S.C. § 343(r)(1)(B) & (r)(3). Thus, "medical foods"—foods that are formulated to meet the needs of individuals with diseases or conditions that may benefit from ingestion and/or clinical management by specialized foods[1]—are not "drugs" within the meaning of the FDCA.

III. The Guidance's Imposition of IND Requirements on Food Is Unauthorized

Congress authorized FDA to impose its IND requirements on "drugs intended for investigational use." 21 U.S.C. § 355i. Regardless whether a substance that is regularly ingested by humans as food could be classified as a "drug," it cannot possibly be deemed an "investigational drug" as that term has long been understood by FDA. If such a food really were an "investigational drug," FDA would be taking steps to prevent its marketing as an unapproved new drug. Accordingly, FDA lacks any statutory basis for seeking to require a manufacturer to submit an IND application before undertaking a clinical investigation of a food.

Moreover, the Guidance has badly misinterpreted the exception for "food" set forth in 21 U.S.C. § 321(g)(1)(C)'s definition of a "drug." Indeed, the appeals court decision upon which FDA relies for its interpretation of § 321(g)(1)(C), *Nutrilab v. Schweiker*, 713 F.2d 335 (7th Cir.

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[1] *See* 21 U.S.C. § 360ee(b)(3) (defining medical food as "a food which is formulated to be consumed or administered enternally 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.").

1983), cuts directly against FDA's position. As *Nutrilab* explains, Congress added § 321(g)(1)(C) to the FDCA to expand the definition of "drug" because:

> [C]ertain articles intended by manufacturers to be used as drugs did not fit within the 'disease' requirement of Section 321(g)(1)(B). Obesity in particular was not considered a disease. Thus 'anti-fat remedies" marketed with claims of "slenderizing effects" had escaped regulation under the prior definition.

713 F.3d at 336. By adding Part C to the definition, Congress intended to extend "drug" regulation to products that are not treatments for disease but that nevertheless are "intended to affect the structure or any function of the body of man."

In doing so, however, Congress very carefully excluded "food" from the expanded definition. The FDCA provides a common-sense definition of "food": it is defined (somewhat circularly) as meaning "(1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article." 21 U.S.C. § 321(f). In other words, any article "used for food or drink for man or other animals" is exempt from Part (C)'s expanded definition of a "drug." In *Nutrilab*, the article in question was a so-called "starch blocker" intended to help with weight loss. The Seventh Circuit determined that the starch blockers did not qualify as "food" because they were not commonly "used for food or drink by man" but rather were only consumed "for their ability to block the digestion of food and aid in weight loss." 713 F.3d at 339. The court interpreted the phrase "used for food or drink by man" to mean "consumed primarily for taste, aroma, or nutritive value," and it concluded that the starch blockers did not meet that definition because no one consumed them as part of a regular meal—or for any reason other than weight loss. *Id.*

In other words, *Nutrilab* teaches—contrary to the position set forth by FDA in the Guidance—that a substance is a food if it is regularly consumed as part of human meals. The substances discussed by FDA in Part VI(D)(2) & (3) of the Guidance—conventional food and medical food—undeniably meet that definition; they are regularly consumed by humans as part of daily nutrition. As such, they do not qualify as "drugs" under Part (C) and thus cannot be made subject to § 355i's IND requirements.

The Guidance provides the following illustration of situations in which a clinical study of a conventional food would or would not require an IND:

> [A] clinical study may be performed to evaluate the tolerability of a food in a specific susceptible population, including individuals with a disease. In such an evaluation, biological parameters affected by the disease may need to be assessed in order to establish tolerance. For example, the administration of high intensity sweeteners to diabetic patients to establish no adverse effect on HbA1c levels on the administration of a novel food protein ingredient to a potentially allergic population to establish lack of allergic reactivity in this population would not require an IND. However, if the intent of the study was to demonstrate an effect of the food in decreasing HbA1c levels in diabetic patients or an effect of the food to desensitize or raise levels of allergic reactivity in sensitive individuals, the study would require an IND.

Guidance at 14. But the Guidance makes no effort to explain why FDA believes that an IND would be required in the latter situation and not the former, and none is readily apparent. Indeed, by referring to the substance being investigated as a "food," FDA is conceding that the substance cannot be deemed a drug under § 321(g)(1). Moreover, if the food is commonly being consumed by humans for taste, aroma, or nutritive value, then it quite clearly is not an "investigative drug" and thus not a product over which FDA has been granted IND authority.

The Guidance appears to view FDA's IND authority as a right to grant licenses to engage

in clinical research. That view is a misreading of § 355i. The purpose of that statute is to permit the distribution of products that, but for special permission from FDA, could not be marketed at all because they lack an approved NDA. Section 355i authorizes FDA to grant such permission because clinical trials of unapproved drugs could not otherwise take place; at the same time, § 355i authorizes FDA to use its IND authority to exercise close supervision over the research process. But § 355i is wholly inapplicable to foods, which can be freely marketed without any need for special permission from FDA and thus are not subject to FDA's IND authority.

If the Guidance's view were correct, then a manufacturer's decision to initiate a clinical study would transform all of its inventory into unapproved new drugs and would bar all sales until such time as the manufacturer gained approval for an NDA. FDA, however, appears unwilling to follow its theory to it logical conclusion. It appears to be quite content to permit continued marketing of the food while the clinical study proceeds, and only deems the product to be a "drug" for purposes of imposing IND requirements. Moreover, the "drug" status instantly vanishes the moment the study is completed. The Guidance's failure to provide any coherent theory regarding how a food is transformed into a drug for some but not all purposes, based solely on initiation of a clinical study, is a strong indication that the Guidance is inconsistent with FDA's statutory mandate.

The Guidance's discussion of medical foods is equally implausible. It states without explanation, "an investigation intended to evaluate the effects of a medical food on a disease would require an IND." Guidance at 14. But in the absence of evidence that the investigation was undertaken for the purpose of supporting a subsequent NDA that would allow the marketing

of the medical food for a specific therapeutic effect, FDA has no statutory basis for invoking its IND authority.

IV. FDA Adopted the Guidance in Violation of the APA

FDA regulations have long understood that the agency's IND requirements apply only to investigational drugs. *See* 21 C.F.R. Part 312. That understanding is consistent with a straightforward reading of 21 U.S.C. § 355i. The Guidance seeks to change that understanding, by applying the IND requirements to food that is already being sold to the public (and thus cannot plausibly be deemed "investigational") simply because someone plans to undertake a clinical study of the food's physiological effects on the human body.

As demonstrated above, the Guidance's new, vastly expanded understanding of FDA's IND authority is inconsistent with the FDCA. But even if the new understanding were a plausible interpretation of the FDCA (which it is not), it unquestionably is inconsistent with FDA's prior understanding of § 355i (as evidenced by existing regulations). Under those circumstances, the APA required FDA to comply with the formal notice-and-comment requirements set forth in 5 U.S.C. § 553(b) & (c) before adopting the new understanding. FDA unquestionably did not comply with those requirements.

The APA's formal notice-and-comment requirements do not apply to mere "interpretive" rules that do no more than attempt to interpret ambiguous provisions contained in federal statutes and agency regulations. However, the Guidance cannot plausibly be labeled a mere interpretive rule. A rule is "legislative" (and thus subject to notice-and-comment procedures) if the rule "effectively amends a prior legislative rule." *Am. Mining Cong. v. Mine Safety & Health Admin,*

995 F.2d 1106, 1112 (D.C. Cir. 1993). As the D.C. Circuit has explained, unless an agency action that modifies its prior interpretation of a formal regulation is subject to notice-and comment rulemaking requirements, "the agency could evade its notice and comment obligation by 'modifying' a substantive rule that was promulgated by notice and comment rulemaking." *Syncor Int'l Corp. v. Shalala*, 127 F.3d 90, 94-95 (D.C. Cir. 1997) (quoting *Paralyzed Veterans of America v. D.C. Arena, L.P.*, 117 F.3d 579, 586 (D.C. Cir. 1997)). In this instance, the Guidance amounted to a "legislative rule" because it amended FDA's previous understandings regarding the scope of its IND authority. Under those circumstances, the Guidance is invalid because it was not issued in compliance with the APA.

CONCLUSION

WLF urges FDA to comply with the FDCA and the APA by withdrawing those portions of the Guidance that relate to customary food and medical food.

Sincerely,

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